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Megestrol acetate for treatment of anorexia-cachexia syndrome (Review)

Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Martí S

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[Intervention Review]

Megestrol acetate for treatment of anorexia-cachexia syndrome

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ABSTRACT

Background

This is an updated version of a previously published review in *The Cochrane Library* (2005, Issue 2) on 'Megestrol acetate for the treatment of anorexia-cachexia syndrome'. Megestrol acetate (MA) is currently used to improve appetite and to increase weight in cancer-associated anorexia. In 1993, MA was approved by the US Food and Drug Administration for the treatment of anorexia, cachexia or unexplained weight loss in patients with AIDS. The mechanism by which MA increases appetite is unknown and its effectiveness for anorexia and cachexia in neoplastic and AIDS (acquired immunodeficiency syndrome) patients is under investigation.

Objectives

To evaluate the efficacy, effectiveness and safety of MA in palliating anorexia-cachexia syndrome in patients with cancer, AIDS and other underlying pathologies.

Search methods

We sought studies through an extensive search of electronic databases, journals, reference lists, contact with investigators and other search strategies outlined in the methods. The most recent search for this update was carried out in May 2012.

Selection criteria

Studies were included in the review if they assessed MA compared to placebo or other drug treatments in randomised controlled trials of patients with a clinical diagnosis of anorexia-cachexia syndrome related to cancer, AIDS or any other underlying pathology.

Data collection and analysis

Two independent review authors conducted data extraction and evaluated methodological quality. We performed quantitative analyses using appetite and quality of life as a dichotomous variable, and analysed weight gain as continuous and dichotomous variables.

Main results

We included 35 trials in this update, the same number but not the same trials as in the previous version of the review. The trials comprised 3963 patients for effectiveness and 3180 for safety. Sixteen trials compared MA at different doses with placebo, seven trials compared different doses of MA with other drug treatments and 10 trials compared different doses of MA. Meta-analysis showed a benefit of MA compared with placebo, particularly with regard to appetite improvement and weight gain in cancer, AIDS and other underlying conditions, and lack of benefit in the same patients when MA was compared to other drugs. There was insufficient information to define the optimal

dose of MA, but higher doses were more related to weight improvement than lower doses. Quality of life improvement in patients was seen only when comparing MA versus placebo but not other drugs in both subcategories: cancer and AIDS. Oedema, thromboembolic phenomena and deaths were more frequent in the patients treated with MA. More than 40 side effects were studied.

Authors' conclusions

This review shows that MA improves appetite and is associated with slight weight gain in cancer, AIDS and in patients with other underlying pathology. Despite the fact that these patients are receiving palliative care they should be informed of the risks involved in taking MA.

PLAIN LANGUAGE SUMMARY

Megestrol acetate for treatment of anorexia-cachexia syndrome

Anorexia-cachexia syndrome (ACS) is a common clinical problem characterised by loss of appetite and weight loss. It is common in patients who suffer from advanced cancer, AIDS and some other conditions. At present, there is no cure for ACS.

Megestrol acetate (MA) is classified as a female hormone and is taken by mouth. It is currently used to improve appetite and to increase weight in ACS.

This updated review shows that:

- MA improves appetite and has a small effect on weight gain;

- MA does not improve quality of life;

- side effects are more frequent in patients treated with MA.

This review shows that MA is associated with an increased risk of blood clots (which may result in swelling, pain or redness of one extremity and not the other, sudden difficulty in breathing, severe headache or vision changes), fluid retention (resulting in swelling of the feet or hands) and death.

In patients who take MA, approximately one in four will have an increase in their appetite, one in 12 will have an increase in their weight and one in 23 will die.

Limited data are available regarding the safety of using MA, especially in the long term.

Summary of findings for the main comparison. Megestrol acetate for cachexia anorexia syndrome

Megestrol acetate for cachexia anorexia syndrome

Patient or population: cachexia anorexia syndrome
Settings: cancer patients, AIDS patients and patients with other underlying conditions
Intervention: megestrol acetate

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Megestrol acetate				
Appetite improvement compared with placebo Subjective sense of appetite, responses to follow-up questionnaire Follow-up: mean 4 to 12 weeks	**Moderate**		**RR 2.19** (1.41 to 3.4)	699 (5 studies)	⊕⊝⊝⊝ **very low**[1,2,3]	NNTB = 4 (95% CI 2 to 11)
	214 per 1000	**469 per 1000** (302 to 728)				
Weight improvement compared with placebo % of patients that improved their weight in kg Follow-up: mean 4 to 12 weeks	**Study population**		**RR 1.51** (1.08 to 2.11)	1106 (10 studies)	⊕⊝⊝⊝ **very low**[3,4,5]	NNTB = 12 (95% CI 6 to 69)
	246 per 1000	**329 per 1000** (260 to 408)				
	Moderate					
	233 per 1000	**312 per 1000** (247 to 387)				
Appetite improvement compared to other drugs Questionnaire of appetite rating Follow-up: median 8 weeks	**Study population**		**RR 1.03** (0.64 to 1.67)	475 (1 study)	⊕⊕⊝⊝ **low**[6,7]	NNTB = NS
	325 per 1000	**335 per 1000** (208 to 543)				
	Moderate					
	325 per 1000	**335 per 1000** (208 to 543)				
Weight improvement compared to other drugs	**Study population**		**RR 1.66** (1.09 to 2.52)	1131 (7 studies)	⊕⊝⊝⊝	NNTB = 22 (95% CI 9 to 159)

% of patients that improved their weight in kg Follow-up: mean 8 to 15 weeks	**72 per 1000**	**119 per 1000** (78 to 180)			**very low**[3,8,9,10]	
	Moderate					
	57 per 1000	**95 per 1000** (62 to 144)				
Deaths Follow-up: mean 2 to 15 weeks	**Study population**		**RR 1.42** (1.04 to 1.94)	1307 (10 studies)	⊕⊖⊖⊖ **very low**[11,12,13,14]	NNTH = 23 (95% CI 10 to 200)
	102 per 1000	**146 per 1000** (107 to 200)				
	Moderate					
	48 per 1000	**69 per 1000** (50 to 94)				
	High					
	0 per 1000	**0 per 1000** (0 to 0)				
Thromboembolic phenomena including thrombophlebitis Follow-up: mean 4 to 16 weeks	**Moderate**		**RR 1.84** (1.07 to 3.18)	1544 (11 studies)	⊕⊖⊖⊖ **very low**[13,15,16]	NNTH = 55 (95% CI 22 to 385) NNTH = 11 (95% CI 4 to 77) NNTH = 2 (95% CI 1 to 15) [17]
	100 per 1000	**191 per 1000** (113 to 323)				
	High					
	500 per 1000	**955 per 1000** (565 to 1000)				
Oedema Follow-up: mean 2 to 12 weeks	**Study population**		**RR 1.36** (1.07 to 1.72)	2182 (12 studies)	⊕⊖⊖⊖ **very low**[18,19]	NNTH = 28 (95% CI 4 to 143)
	104 per 1000	**141 per 1000** (111 to 179)				
	Moderate					
	109 per 1000	**148 per 1000** (117 to 187)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval;**NNTB:** number needed to treat for an additional beneficial outcome; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Adequate sequence generation was low risk only in Feliu 1992. Allocation concealment was unclear in all studies. In three out of five studies appetite was rated as high risk of bias because it could be sensitive to lack of blinding.
[2] The two different subcategories (cancer and AIDS patients) showed similar effects. Heterogeneity was moderate (I^2 = 59%) and is due to the study of Schmoll 1991. Heterogeneity without this study became low (I^2 = 39%). The confidence intervals of the studies overlap.
[3] Doses of MA were very different (960 mg, 800 mg, 480 and 160 mg) compared with placebo.
[4] Eight out of 10 studies were rated as unclear for adequate sequence generation; only one study was rated as low risk for allocation concealment. All studies were rated as low risk of bias for blinding. Schmoll 1991, Schmoll 1992 and Von Roenn 1994 were rated low risk because lack of blinding is not related to weight. Only one study was rated as high risk of bias for incomplete outcome data. All trials were rated unclear with respect to freedom from 'other bias'.
[5] The effect is quite similar and CI values overlap for most of the studies. However, two studies (Feliu and Schmoll) showed greater effects and the CI was quite wide. The study of Yeh 2000 showed different results in patients with geriatric cachexia to patients with neoplasia and AIDS. Heterogeneity was moderate (I^2 = 53%).
[6] The only study found was rated as unclear risk of bias for adequate sequence generation and allocation concealment. It was not a blinded study and was rated as high risk of bias for the blinding item.
[7] We pooled the results of two comparisons: MA versus dexamethasone and fluoxymesterone.
[8] All studies except Mwamburi 2004 were rated as unclear risk of bias for adequate sequence generation and allocation concealment study.
[9] Heterogeneity was moderate (I^2 = 51%) but heterogeneity between subgroups was high. The effect seemed to be different in cancer and AIDS patients. The CI values overlapped for most of the studies. Cancer patients showed a better response for weight.
[10] The CI interval (9 to 159) is too wide to establish a true effect.
[11] Only one study out of seven was rated as low risk of bias for adequate sequence generation and allocation concealment.
[12] Although the I^2 in both subgroups was 0% and the overall I^2 was low (6.4%), patients with cancer, AIDS and other pathologies were quite different. Moreover the comparator included placebo and other drugs.
[13] Different doses of MA in each subgroup.
[14] The CI interval for the NNT (10 to 200) is too wide to establish a true effect.
[15] Adequate sequence generation was rated as low risk in three out of 10 trials and allocation concealment was rated low risk only in two out of 10.
[16] Although the I^2 in both subgroups was 0% and the overall I^2 was low (0%), patients with cancer, AIDS and other pathologies were quite different. Moreover the comparator included placebo and other drugs.
[17] The first NNTH was calculated with data of this Systematic Review. The second NNTH was calculated with an expected value of 0.10% and the last was calculated with an expected rate of 50%.
[18] Only three out of 11 trials were rated as low risk for adequate sequence generation. Only two out of 11 trials were rated as low risk for allocation concealment.
[19] Although the I^2 in both subgroups was 0% and the overall I^2 was low (0%), patients with cancer, AIDS and other pathologies such as COPD were quite different. Moreover the comparator included placebo and other drugs.

BACKGROUND

Description of the condition

This review is an update of a previously published review in *The Cochrane Library* (2005, Issue 2) on megestrol acetate for anorexia-cachexia syndrome. Anorexia-cachexia syndrome is a common clinical problem that substantially impacts upon the quality of life and survival of affected patients. It is characterised by loss of appetite, weight loss and tissue wasting, accompanied by a decrease in muscle mass and adipose tissue, impoverishing quality of life and often preceding the patient's death (Nelson 1994; Splinter 1992).

More than two-thirds of patients dying from advanced cancer suffer from anorexia-cachexia syndrome (Argilés 2001). Anorexia-cachexia syndrome is also described in other pathologies such as in acquired immune deficiency syndrome (AIDS), anorexia nervosa, degenerative illnesses of the central nervous system and terminally ill patients (Von Roenn 1996). Incidence is variable and difficult to determine but in general the syndrome may occur in 15% to 40% of patients with cancer, and in more than 80% of patients with advanced illness (Bruera 1992).

The mechanism that causes cachexia is poorly understood, but inflammatory cytokines probably have a role, such as tumour necrosis factor-alpha (which is also nicknamed 'cachexin' or 'cachectin'), angiotensin II and glucocorticoids, interferon gamma and interleukin 6, as well as the tumour-secreted proteolysis-inducing factor (Tisdale 2009). Ghrelin levels are also high in patients who have cancer-induced cachexia (Wolf 2006).

An international consensus statement defines cachexia as weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current body weight and height (body mass index (BMI) < 20 kg/m^2) or skeletal muscle mass (sarcopaenia) (Fearon 2011).

Description of the intervention

Early intervention and attention to nutritional status are essential in patients with anorexia-cachexia syndrome. Pharmacological interventions for neoplastic cachexia include drugs that stimulate the appetite: megestrol acetate (MA) and dronabinol; cytokine inhibitors (such as cyproheptadine, thalidomide, pentoxifylline and an eicosapentaenoic acid (EPA)); and anabolic agents such as nandrolone decanoate, oxandrolone and corticosteroids (Balog 1998). EPA seems to suppress well-characterised mediators of cancer-associated wasting, including interleukin-6, an inflammatory cytokine. It also acts over the proteolysis-inducing factor, another well-described mediator (Barber 1999; Wigmore 1997).

MA is a synthetic progestogen agent. It was first synthesised in England in 1963. Developed as an oral contraceptive, the agent was first tested in the treatment of breast cancer in 1967 and, later on, for the treatment of endometrial cancer. MA is currently used to improve appetite and to increase weight in cancer-associated anorexia. From September 1993, MA was approved by the Food and Drug Administration (FDA) in the USA for the treatment of anorexia, cachexia or unexplained weight loss in patients with AIDS. In addition, there are recent reports of the drug being used to improve the quality of life of elderly patients with cachexia. A possible role in anorexia nervosa has also been proposed (Yeh 2000).

MA is only available as a tablet of 20 to 40 mg or liquid form (200 mg or 625 mg/5ml MA). A great variability in dosage is observed in the scientific literature, ranging from 100 mg to 1600 mg per day (Tchekmedyian 1992; Von Roenn 1994). The liquid form is usually dosed at 800 mg per day and the oral form at four tablets per day. The recommended duration of treatment is six weeks or more. MA is considered a relatively non toxic drug with a low incidence of adverse effects, such as fluid retention, venous thrombosis, diarrhoea, rash, impotence, pruritus, increased blood sugar level and headache (Loprinzi 1990a; Vadell 1998; Von Roenn 1994). The recommended adult initial dosage of MA oral suspension in HIV patients is 800 mg/day (20 ml/day); clinically effective dosages are expected to range from 312.5 to 625 mg daily. In patients with neoplastic disease the most common dosages used range from 480 to 600 mg daily.

How the intervention might work

Although the mechanism by which MA increases appetite is unknown, most hypotheses point to action on cytokines, which inhibit the action of tumour necrosis factor on fatty tissue and its products. Currently, interest is especially focused on its effectiveness in the treatment of anorexia and cachexia in neoplastic and AIDS patients. Studies at the Mayo Clinic and The North Central Cancer Treatment Group Study have reported and reviewed multiple placebo-controlled, randomised, double-blind clinical trials of MA and other drugs for the improvement of anorexia-cachexia syndrome in all types of cancer (Jatoi 2004; Loprinzi 1990a).

Why it is important to do this review

This is an update of a previous systematic review. In this update we identified new trials and found that more diseases have begun to be treated with MA. We focused on the adverse events of MA as main outcomes.

OBJECTIVES

1. To evaluate the effectiveness and safety of MA in palliating anorexia-cachexia syndrome in subgroups of patients with cancer, AIDS and other underlying pathologies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) which may be double-blind, single-blind or unblinded.

In the previous version of the review we included some cross-over studies. However, in the current update we decided not to include these studies, because the time between the two phases is too short to be certain whether any adverse event or outcome, such as weight or appetite, is due to MA or placebo. Moreover, treating with MA or placebo in the first phase could result in groups in the second phase not having the same basal characteristics. Finally, due to the fact that these patients are very frail and have high mortality, the number of patients in such studies could be too low.

Types of participants

Patients with a clinical diagnosis of anorexia-cachexia related to cancer, AIDS or another underlying pathology (independent of gender, age or race) were included. We decided to include only trials with patients who clearly had some previous weight loss or definition of cachexia-anorexia syndrome.

Types of interventions

The review focuses on the following treatment comparisons:

- MA at any dose versus placebo;
- MA at any dose versus other active drug treatments (stimulants of appetite such as dronabinol, cytokine inhibitors such as cyproheptadine, eicosapentaenoic acid (EPA) and anabolic agents such as nandrolone decanoate and corticosteroids);
- MA at different doses.

Types of outcome measures

We assessed the following outcome measures.

Primary outcomes

- Weight gain, measured as a dichotomous variable (number of patients who gained weight) and as a continuous variable in kg (difference between baseline and the end of treatment).
- Improvement in quality of life by means of a validated instrument, or with scales of functional scores (e.g. Karnofsky Index and performance status) that measure the well-being status of the patient. The quality of life measures will depend on the instrument used, e.g. patient assessments using a Likert-type scale based on patients' statements and self report questionnaires, or the use of the Spitzer Index of quality of life, completed by the clinician.
- Adverse effects: we analysed these as the number of patients who suffered an event described as a side effect by the authors of each study.

Secondary outcomes

- Appetite increase, expressed as a dichotomous variable (number of patients who experienced appetite increase) or a continuous variable.
- Measurements of the mid-arm circumference and triceps skin fold thickness by anthropometry, as a percentage of the differences in the total body muscle and fat mass.
- Deaths.

Study withdrawals and drop-outs were analysed as:

- total number of drop-outs and withdrawals;
- number of withdrawals due to lack of effectiveness of treatment;
- number of withdrawals due to adverse effects.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to identify relevant studies:

- Cochrane Pain, Palliative and Supportive Care Group Trials Register (2011, Issue 3) (see Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3);
- MEDLINE from 1966 to May 2012 (see Appendix 2);
- EMBASE from 1980 to May 2012 (see Appendix 3).

We combined the general strategy for identifying RCTs in MEDLINE with a strategy designed to retrieve trials of MA for cachexia. For the identification of studies to include in or consider for this review, we developed detailed search strategies for each database searched.

Searching other resources

We checked lists of references from systematic reviews of MA and from the included studies to identify further trials.

Studies were not excluded on the basis of language or publication status (published, unpublished, in press and in progress).

We sought additional data from published trials by contacting authors. We consulted the information made available by the main researchers/sponsors.

We also reviewed information on the clinical trial meta-register database (http://www.controlled-trials.com/mrct/).

Data collection and analysis

Selection of studies

Two review authors independently reviewed the titles and abstracts of studies identified in the search to assess which studies might potentially meet the inclusion criteria. Where there was doubt, we acquired the full article for further inspection. We then obtained potential studies identified by this process and two authors independently screened them to see if they met the review criteria. We created an Excel spreadsheet. We did not need to resolve any disagreements through discussion.

Data extraction and management

Two authors independently extracted data using a data collection form (in Excel). We checked any disagreements in the data collection and we reviewed the studies again only if there was a mismatch between them. We collected, when possible, data for intention-to-treat populations as raw numbers, summary measures with standard deviations, confidence intervals and P values of outcomes reported and compiled these into the Excel spreadsheet.

Assessment of risk of bias in included studies

According to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, we assessed the risk of bias by creating a summary of 'Risk of bias' table (Higgins 2011).

The main criteria used to measure the risk of bias included: blinding of participants, allocation concealment, random sequence generation, incomplete outcome data, selective reporting of outcomes and other bias (early stopping of trials or imbalance in the baseline of people in the groups). We explicitly judged the risk of bias in each study on the basis of the following criteria: low risk of bias, high risk of bias, unclear risk of bias (either lack of information or uncertainty over the potential bias). These criteria were included in the tables. Disagreements were resolved by discussion between the two review authors. If needed, a third review author was available for discussion in case of unresolved disagreements.

We also evaluated the methodological quality of the studies using a validated scale called the Oxford Quality Scale (Jadad 1996), according to the following domains: concealment of allocation, double-blinding, intention-to-treat analysis and loss to follow-up. We also assessed each study using the zero to five-point scale described by Jadad 1996, as summarised below.

1. Was the study described as randomised? (1 = yes; 0 = no).
2. Was the study described as double-blind? (1 = yes; 0 = no).
3. Were withdrawals and drop-outs described? (1 = yes; 0 = no).
4. Was the method of randomisation well-described and appropriate? (1 = yes; 0 = no); deduct one point if inappropriate.
5. Was the double-blinding well-described and appropriate? (1= yes; 0 = no); deduct one point if inappropriate.

Measures of treatment effect

We use the risk ratio (RR) because it is more intuitive (Boissel 1999) than the odds ratio and because odds ratios tend to be interpreted as RR by clinicians (Higgins 2011). We used the risk difference to quantify the number needed to treat for an additional beneficial outcome (NNTB) (Laupacis 1988). For continuous data we used mean differences (MD) when the results were measured in the same way in different studies. We used standardised mean differences (SMD) when the results obtained were conceptually the same but used different measurement scales. We recorded the central estimate (mean) and standard deviation. Where these were not directly stated we calculated them from the standard error.

Unit of analysis issues

Most of the studies used a simple parallel-group design, in which participants are individually randomised to one of two intervention groups. Unit of analysis was not an issue in this review.

Dealing with missing data

We carried out an intention-to-treat analysis. Everyone allocated to the intervention was counted whether they completed the follow-up or not. We have assumed that those who dropped out had no change in their outcome. This rule is conservative concerning response to treatment, because it assumes that those discontinuing the studies would not have responded. It is not conservative concerning adverse effects, but we felt that assuming that all those leaving early would have developed side effects would overestimate risk.

When published data were missing, incomplete or inconsistent with RCT protocols or meeting abstracts, we asked for further information from the authors/manufacturers. We have only excluded abstracts of studies that are interim reports of studies that have not yet finished recruiting.

Assessment of heterogeneity

We explored heterogeneity between the trials using the Chi^2 test for heterogeneity with a 10% level of significance, and the I^2 statistic. We complied with the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, which determine that an I^2 value of 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity (Deeks 2008).

Assessment of reporting biases

We planned to explore reporting bias using funnel plots if we had a meta-analysis of 10 or more studies. The items in the assessment biases were: 1) Allocation 2) Blinding 3) Incomplete outcome data 4) Selective reporting 5) Other potential source of bias

Data synthesis

We explored the need to analyse the results according to a fixed or random-effects analysis (Laird 1990). In the event of significant heterogeneity we may have made a decision not to present combined result (Schulz 1993). We calculated the number needed to treat for an additional beneficial outcome (NNT or NNTB) and the number needed for an additional harmful outcome (NNTH). We used the mean difference to calculate the benefit (absolute change expressed as both a percentage and in its original units) for continuous outcomes such as Karnofsky Index score or weight gain.

For dichotomous variables, we computed treatment effects as risk ratios (RR) with 95% confidence intervals (CI). For continuous variables such as weight gain or appetite gain we calculated differences in means and their 95% CI (mean difference (MD)) and for quality of life (including different scales), we calculated differences in means and their 95% CI (standardised mean difference (SMD)). Only validated scales with a normal distribution were included in the analysis. We determined validity of the scale from the psychometric properties of the instrument as described in the trial by the review authors.

We used a random-effects model in the analysis. We analysed statistical heterogeneity between studies with the Chi^2 test, using $P < 0.1$ as a cut-off value to represent the presence of significant heterogeneity. When a high level of heterogeneity was detected, we made attempts to identify the sources of the heterogeneity and performed subsequent meta-analysis using a random-effects model.

We used the 'Grades of Recommendation, Assessment, Development and Evaluation' approach developed by the GRADE Working Group for grading the quality of evidence. The GRADE approach specifies four levels of quality. The highest quality rating is for randomised trial evidence. Review authors can, however, downgrade randomised trial evidence to moderate, low or even very low-quality evidence, depending on the presence of five specific factors (Higgins 2011, chapter 11).

We used GRADE software to provide an overall grading of the quality of the evidence by outcome.

Subgroup analysis and investigation of heterogeneity

If heterogeneity was detected we planned to carry out subgroup analysis (Yusuf 1991) and/or a meta-regression in order to explain it (Thompson 1999).

Subgroup analyses were planned for:

- patients with AIDS;
- patients with cancer;
- patients with other underlying disease (elderly, chronic obstructive pulmonary disease (COPD), cardiac heart failure);
- high doses of MA (=> 800 mg/d) versus low doses of MA (< 800 mg/d);

- duration of trial, size and methodological quality.

Sensitivity analysis

In order to explore the impact of specific factors on the meta-analysis results, we undertook sensitivity analyses with:

- studies of high methodological quality, defined as studies with appropriate concealment of allocation, appropriate blinding and analysis by intention-to-treat (ITT);
- studies where patients received more than six weeks of treatment.

We carried out the statistical analyses using the statistical package in Review Manager 5.1.6 (RevMan 2011).

RESULTS

Description of studies

Results of the search

Searching the electronic databases identified:

- 385 references in MEDLINE;
- 401 references in EMBASE; and
- 164 references in the Cochrane Central Register of Controlled Trials (CENTRAL).

We located an additional reference through Google and one more through a researcher who was involved in one trial that was never published.

We updated the first search to May 2012 (see Appendix 2; Appendix 3; Appendix 1) and one trial was added (Madeddu 2012).

A flowchart of included studies, according to the PRISMA recommendations, is shown in Figure 1

Figure 1. Study flow diagram.

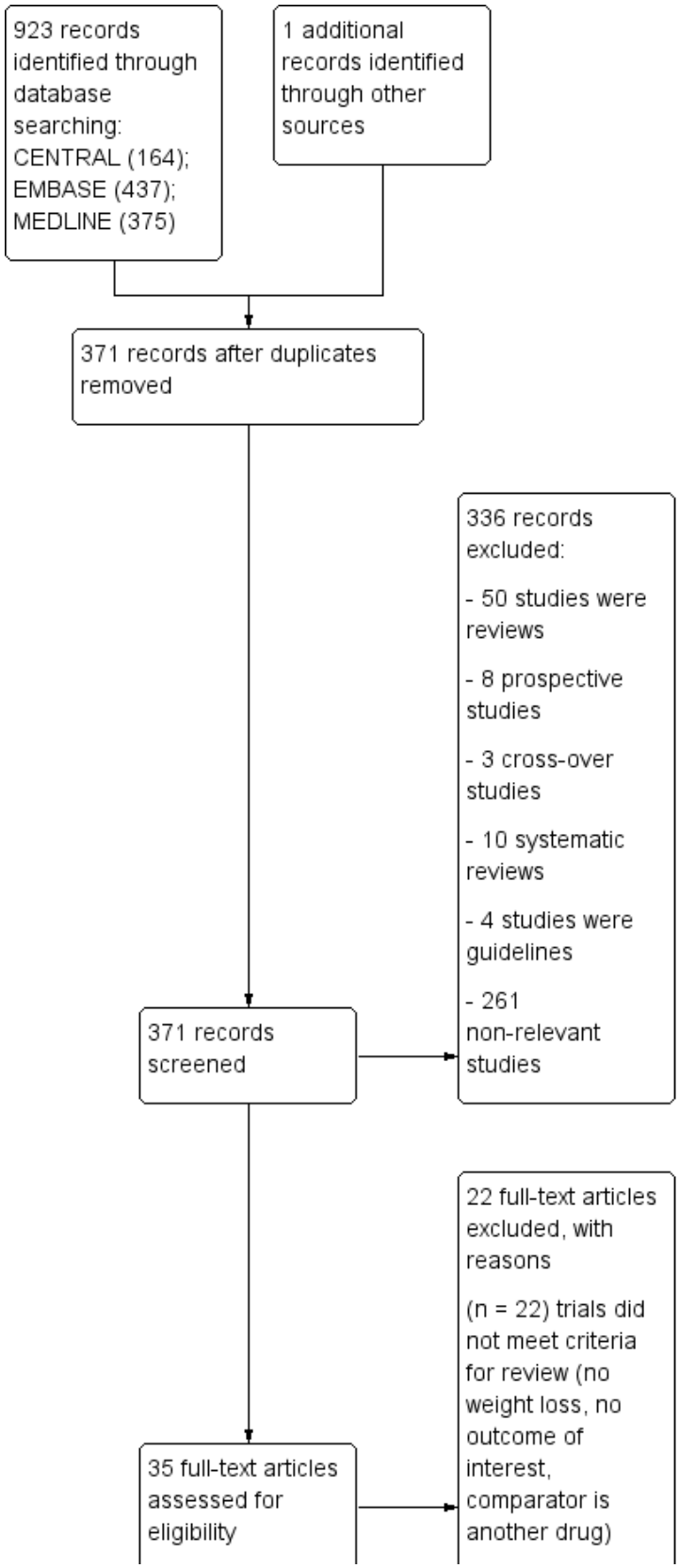
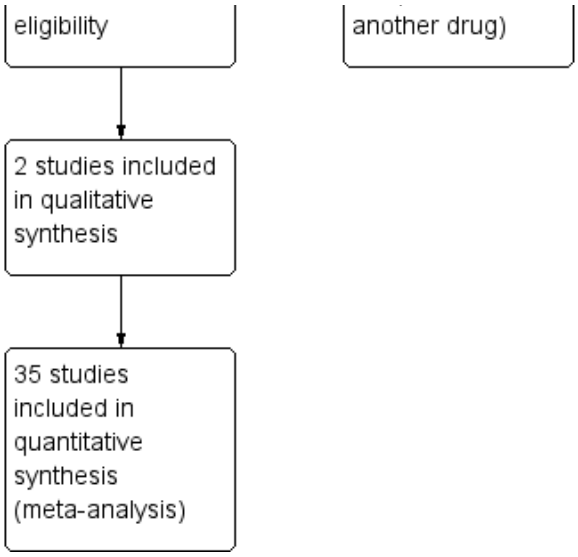


Figure 1. (Continued)



Included studies

We included most of the trials that were in the previous version of the review: Batterham 2001; Beller 1997; De Conno 1998; Eubanks 2002; Feliu 1992; Fietkau 1996; Gambardella 1998; Gebbia 1996; Heckmayr 1992; Jatoi 2002; Jatoi 2004; Loprinzi 1990b; Loprinzi 1994; Loprinzi 1999a; McMillan 1994; Oster 1994; Sancho-Cuesta 1993; Schmoll 1992; Tchekmedyian 1992; Ulutin 2002; Vadell 1998; Von Roenn 1994; Weisberg 2002; Yeh 2000 and included the following new trials: Casado 2008; Giacosa 1997; Herrejon 2011; Lesser 2006; Madeddu 2012; Macbeth 1994; Mwamburi 2004; Schmoll 1991; Summerbell 1992;Timpone 1997; Wanke 2007. Ultimately we included 35 trials, representing 3963 patients studied for effectiveness and 3240 for safety. We could not use the data from the included trials Lesser 2006 and Gambardella 1998. See Characteristics of included studies table.

Many of these citations were replicated across the three databases.

The designs of the 35 trials were as follows:

MA at different doses compared with placebo

Seventeen trials compared MA at different doses with placebo: Beller 1997; Casado 2008; De Conno 1998; Eubanks 2002; Feliu 1992; Fietkau 1996; Herrejon 2011; Loprinzi 1990b; McMillan 1994; Oster 1994; Schmoll 1991; Schmoll 1992; Tchekmedyian 1992; Vadell 1998; Von Roenn 1994; Weisberg 2002; Yeh 2000. In Madeddu 2012 one arm was carnitine plus celecoxib and the second arm was carnitine plus celecoxib plus MA 300 mg/day. In this trial only few safety data were available for the meta-analysis and we decided include it in this comparison.

MA at different doses compared with other treatment drugs

Seven trials compared different doses of MA with other drug treatments. MA was compared with dronabinol in two studies (Jatoi 2002; Timpone 1997); dexamethasone and fluoxymesterone in one study (Loprinzi 1999); nandrolone decanoate in one study (Batterham 2001); cyproheptadine in one study (Summerbell 1992); oxandrolone in two studies (Lesser 2006; Mwamburi 2004); prednisolone in one study (Macbeth 1994) and eicosapentaenoic acid (EPA) in one study (Jatoi 2004).

MA at different doses

Ten trials compared different doses of MA.

- Beller 1997: MA 160 mg versus MA 480 mg
- Casado 2008: MA 160 mg versus MA 960 mg versus placebo
- Gebbia 1996: MA 160 mg versus MA 320 mg
- Heckmayr 1992: MA 160 versus MA 480 mg
- Loprinzi 1994: MA 160 versus MA 480 mg versus MA 800 mg versus MA 1280 mg
- Sancho-Cuesta 1993: MA 160 versus MA 320 mg
- Schmoll 1991: MA 480 mg versus MA 960 mg versus placebo
- Schmoll 1992: MA 480 mg versus MA 960 mg versus placebo
- Ulutin 2002: MA 160 mg versus MA 320 mg
- Vadell 1998: MA 160 mg versus MA 480 mg versus placebo
- Wanke 2007: MA 575 mg versus MA 800 mg

We categorised the included studies according to the healthcare problem of the patient - see Table 1 for a summary.

Patient characteristics

A total of 4234 patients were included in this update.

Patients with any cancer

Twenty-three trials (3428 patients) (Beller 1997; Casado 2008; De Conno 1998; Feliu 1992; Fietkau 1996; Gambardella 1998; Gebbia 1996; Giacosa 1997; Heckmayr 1992; Jatoi 2002; Jatoi 2004; Lesser 2006 Loprinzi 1990b; Loprinzi 1994; Loprinzi 1999; McMillan 1994; Macbeth 1994; Madeddu 2012; Sancho-Cuesta 1993 Schmoll 1991; Schmoll 1992; Tchekmedyian 1992; Ulutin 2002 Vadell 1998) assessed the effectiveness/safety of MA for anorexia-cachexia syndrome in cancer patients where the primary site was:

- lung cancer(1342 patients);
- gastrointestinal and pancreatic cancer(928 patients);

- head and neck cancer(284 patients);
- gynaecological cancer (21 patients);
- non-specified sites(907 patients).

Patients with AIDS

Five trials (475 patients) assessed the effectiveness of MA for anorexia-cachexia syndrome in AIDS patients (Batterham 2001; Mwamburi 2004; Oster 1994; Timpone 1997; Von Roenn 1994).

Patients with other underlying conditions

Four trials (271 patients) assessed the effectiveness of MA for anorexia-cachexia syndrome in patients with the following conditions:

- COPD: two trials with 185 patients (Herrejon 2011; Weisberg 2002);
- cystic fibrosis: one trial with 17 patients (Eubanks 2002);
- elderly: one trial with 69 patients (Yeh 2000).

Dose

Across the studies, the dose of MA ranged from 100 mg per day to 1600 mg per day in at least one of the study arms.

The doses of MA assessed were as follows:

- *400 mg per day or less*

Seventeen trials: (Batterham 2001 400 mg per day; Beller 1997 160 mg per day; De Conno 1998 320 mg per day; Feliu 1992 240 mg per day; Fietkau 1996 160 mg per day; Gebbia 1996 160 mg and 320 mg per day; Giacosa 1997 320 mg per day; Heckmayr 1992 160 mg per day; Herrejon 2011 320 mg per day; Loprinzi 1994 160 mg per day; Madeddu 2012 320 mg/per day Sancho-Cuesta 1993 160 mg per day; Summerbell 1992 40 mg daily on alternate weeks to a maximum of 160 mg daily; Timpone 1997 250 mg per day; Ulutin 2002 160 mg and 320 mg per day; Vadell 1998 160 mg per day; Von Roenn 1994 100 mg and 400 mg per day).

- *480 mg per day*

Seven trials: Beller 1997; Heckmayr 1992; Loprinzi 1994; McMillan 1994; Schmoll 1991; Schmoll 1992; Vadell 1998.

- *575 to 600 mg per day*

Two trials: (Wanke 2007 575 mg per day; Jatoi 2004 600 mg per day).

- *750 to 800 mg per day*

Ten trials: (Timpone 1997 750 mg per day; Jatoi 2002; Loprinzi 1990b; Loprinzi 1994; Loprinzi 1999; Mwamburi 2004; Oster 1994; Von Roenn 1994; Weisberg 2002; Yeh 2000 (all 800 mg per day)).

- *1280 mg per day*

One trial: Loprinzi 1994.

- *1600 mg per day*

One trial: Tchekmedyian 1992.

- One trial in children with cystic fibrosis assessed MA at a dose of 10 mg/kg per day (Eubanks 2002).

Study duration

The study duration ranged from two weeks to 24 weeks. The median trial duration time was eight weeks. Seventeen trials had a duration of 12 weeks or more. (See Characteristics of included studies table).

- Final assessment at two weeks (Beller 1997; De Conno 1998).
- Assessment at four weeks/one month (Gebbia 1996; Heckmayr 1992; Loprinzi 1990b).
- Assessment at six weeks (Fietkau 1996; Tchekmedyian 1992).
- Assessment at eight weeks/two months (Feliu 1992; Jatoi 2002; Herrejon 2011; Macbeth 1994; Mwamburi 2004; Loprinzi 1994; Loprinzi 1999b; Schmoll 1991; Schmoll 1992; Weisberg 2002).
- Assessment at 12 weeks/three months (Batterham 2001; Casado 2008; Jatoi 2004; Lesser 2006; McMillan 1994; Oster 1994; Timpone 1997; Ulutin 2002; Vadell 1998; Von Roenn 1994; Wanke 2007).
- Assessment at 13 to 16 weeks (Madeddu 2012; Summerbell 1992; Yeh 2000).
- Assessment at six months or more (Eubanks 2002; Sancho-Cuesta 1993).

Excluded studies

We excluded a total of 110 studies.

In the present update we excluded the following studies that had been included in the previous review: Bruera 1990(cross-over study); Bruera 1998(cross-over study); Chen 1997 (a trial of patients with head and neck cancers but only 18% were underweight; moreover 11% were overweight); Erkurt 2000 (this study included a proportion of patients without weight loss in the previous six months and in addition patients were not balanced in both arms, specifically while in the MA arm 27% of the patients received oral nutrition support, in the placebo group 72% of patients received it); Lai 1994 (patients did not have cachexia or any weight loss); Marchand 2000 (cross-over study); McQuellon 2002 (patients were not described as patients with cachexia); Rowland 1996 (patients were not described as patients with cachexia and anorexia); and Zeca 1995 (a trial that included patients with cancer and anorexia, but cachexia was not needed as a inclusion criterion).

Risk of bias in included studies

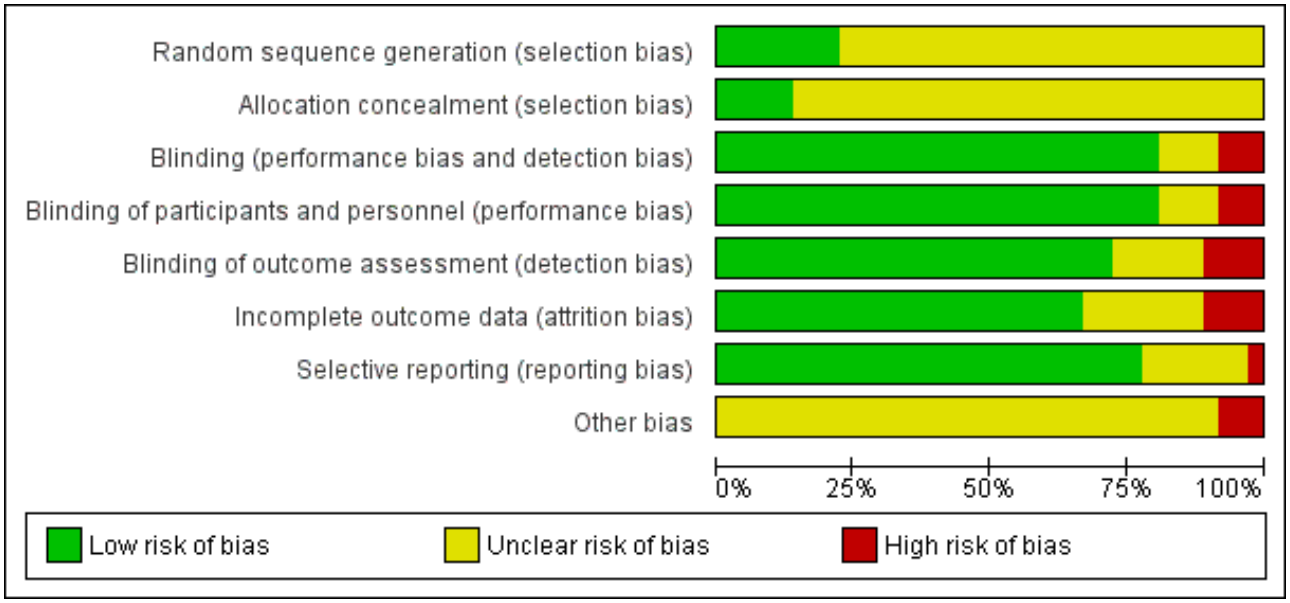
We assessed the methodological quality of the included studies using the Oxford Quality Scale (Jadad 1996). The review authors scored each report independently for quality using the three-item scale described in the Methods section above and agreed a 'consensus' score. The scores for methodological quality are shown in Characteristics of included studies .

Eighteen trials (51%) scored three or more out of a maximum of five: Beller 1997; De Conno 1998; Eubanks 2002; Feliu 1992; Fietkau 1996; Herrejon 2011; Jatoi 2002; Jatoi 2004; Loprinzi 1990b; McMillan 1994; Mwamburi 2004; Oster 1994; Tchekmedyian 1992; Timpone 1997; Vadell 1998; Wanke 2007; Weisberg 2002; Yeh 2000.

Seventeen trials 49% achieved a low score (two points or lower): Batterham 2001; Casado 2008; Gambardella 1998; Gebbia 1996; Giacosa 1997; Heckmayr 1992; Lesser 2006; Loprinzi 1994; Loprinzi 1999a; Macbeth 1994; Madeddu 2012; Sancho-Cuesta 1993; Schmoll 1991; Schmoll 1992; Summerbell 1992; Ulutin 2002; Von Roenn 1994.

The scores of risk of bias are shown in Figure 2

Figure 2. Risk of bias



Allocation

Beller 1997; Herrejon 2011; Tchekmedyian 1992; Timpone 1997 and Wanke 2007 adequately described the methods used to ensure that allocation of participants to treatment groups was concealed. The remaining studies did not report the method used.

Blinding

Eleven studies were not blinded: Batterham 2001; Casado 2008; Gebbia 1996; Giacosa 1997; Heckmayr 1992; Lesser 2006; Loprinzi 1999a; Loprinzi 1999b; Macbeth 1994;Madeddu 2012; Ulutin 2002; Wanke 2007.

Ten more studies were described as blinded but did not describe the methods used to ensure that participants and interacting investigators were unable to differentiate between the treatment and control tablets: Beller 1997; De Conno 1998; Fietkau 1996; Gambardella 1998; Loprinzi 1994; McMillan 1994; Tchekmedyian 1992; Von Roenn 1994; Weisberg 2002; Yeh 2000.

The remaining seven studies were blinded and provided adequate information: Eubanks 2002; Herrejon 2011; Jatoi 2002; Jatoi 2004; Loprinzi 1990b; Oster 1994; Vadell 1998.

We have rated trials that were not blinded as follows: when the main outcome was weight, we decided that this outcome was not likely to the influenced for patients or researchers, so we rated the risk of bias as 'low'. When the main outcome was appetite, we decided that this could be influenced by patients and researchers, and we rated risk of bias as 'high'.

Incomplete outcome data

In Schmoll 1992, withdrawals were higher in the placebo group (44%) than in both MA groups (30%) and explanations were not provided. In Vadell 1998, the rate of withdrawals was very high (only 64 out of 152 initial patients remained in the study after 12 weeks). In both cases we rated risk of bias as 'high'. We rated the remaining studies as low risk, either because of lack of drop-outs or losses in the follow-up or because the number of drop-outs was low and equitably balanced between intervention groups.

Selective reporting

The protocols for the studies were not available (except for Herrejon 2011), which we rated low risk of bias. In view of the fact that the authors only reported data at 12 weeks and not at 24 weeks we rated this a high risk bias in Batterham 2001. We rated the rest of the studies as unclear risk of bias because all the predefined outcomes were available.

Other potential sources of bias

Studies with small group sizes and poor quality (allocation sequence, concealment of allocation or adequate blinding) tend to overestimate efficacy (Kjaergard 2001; Nüesch 2010). In this review, 18 out of 34 trials had a sample size of less than 100 and poor quality; in particular the following: Batterham 2001 (15 patients); De Conno 1998 (48 patients); Eubanks 2002 (17 patients); Fietkau 1996 (61 patients); Gambardella 1998 (30 patients); Giacosa 1997 (28 patients); Heckmayr 1992 (66 patients); Lesser 2006 (74 patients); Madeddu 2012 (60 patients); Macbeth 1994 (75 patients); McMillan 1994 (38 patients); Mwamburi 2004 (40 patients); Schmoll 1991 (55 patients); Schmoll 1992 (91 patients); Summerbell 1992 (14 patients); Timpone 1997 (50 patients); Wanke 2007 (63 patients); and Yeh 2000 (69 patients).

Additionally, we rated three trials as high risk of bias: Macbeth 1994 (stopped early for safety); Summerbell 1992 (discontinued because the recruitment was too slow) and Lesser 2006 (we only have a conference proceeding dated 2006; we have not found any paper with all the relevant data for this trial).

Effects of interventions

See: **Summary of findings for the main comparison** Megestrol acetate for cachexia anorexia syndrome

We meta-analysed data from the included studies in three groups.

- Megestrol acetate (MA) versus placebo
- MA versus other active drug treatments
- MA at different doses

We further categorised the studies as follows.

- Patients with cancer
- Patients with AIDS
- Patients with other underlying pathologies

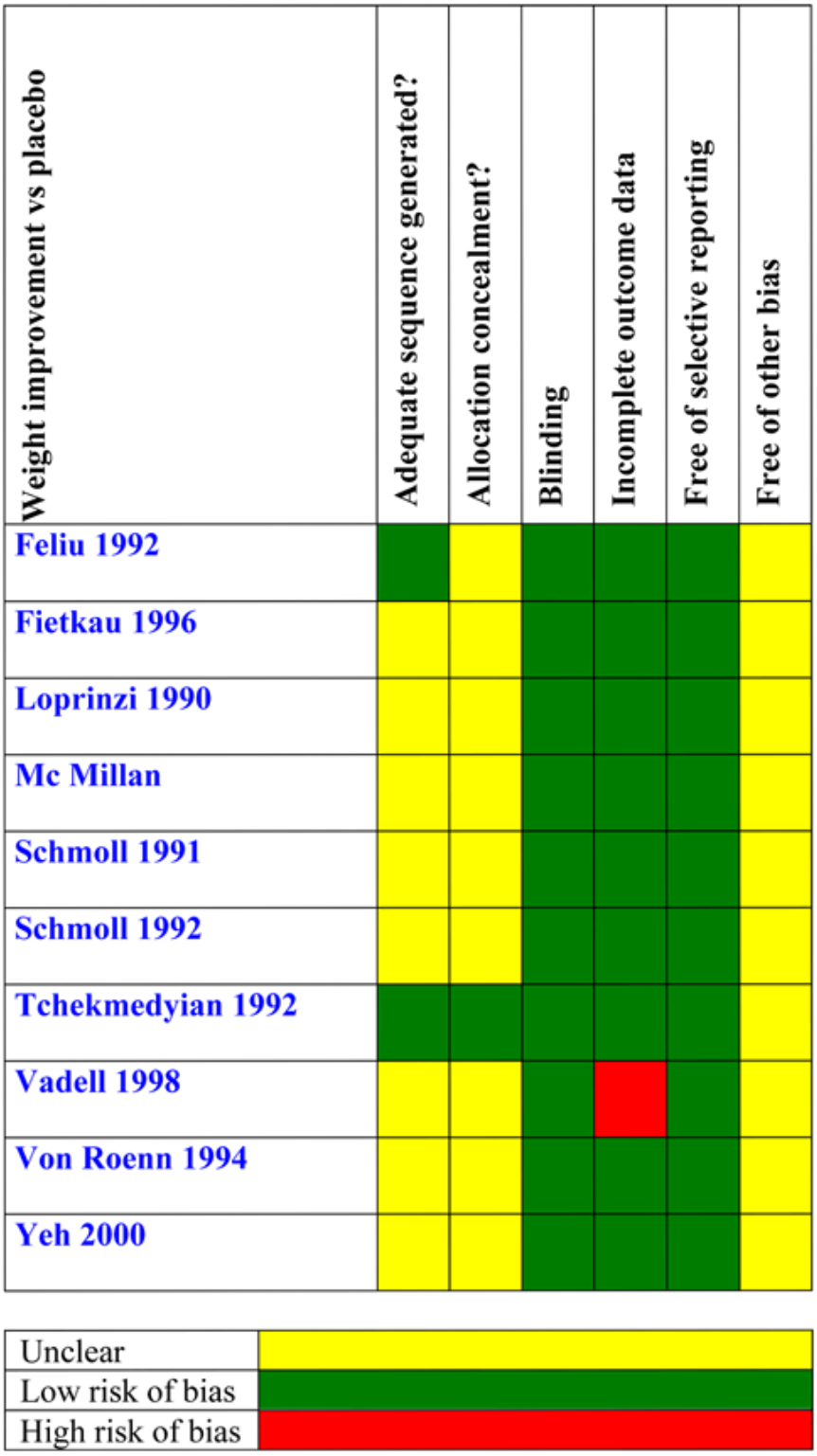
We used risk ratio (RR) to assess quality of life, weight and appetite and used mean difference (MD) for weight and appetite gain as continuous variables. When quality of life was described as a continuous variable we used standardised mean difference (SMD) because this item was reported using different scales (Karnofsky Index, linear analogue self assessment, etc.).

Megestrol acetate versus placebo

Weight gain

The overall results show weight improvement for patients treated with MA (RR 1.51, 95% CI 1.08 to 2.11) (Analysis 1.3). Eight trials were studied. The result for the subcategory of cancer patients was RR 1.55 (95% CI 1.06 to 2.26) (Analysis 1.3). One trial was found for each of the subcategories AIDS and other underlying pathologies. No overall results for these subcategories could be achieved. The quality of the trials for this outcome is shown in Figure 3.

Figure 3.



For weight gain, the overall results show an improvement for patients treated with MA (MD 1.93, 95% CI 0.95 to 2.91) (Analysis 1.4). Both the subcategories cancer patients and patients with other underlying pathologies show improvement (MD 1.63, 95% CI 0.87 to 2.38 and MD 1.47, 95% CI 0.06 to 2.87, respectively) (Analysis 1.4).

We explored heterogeneity between the trials using the Chi^2 test, with a 10% level of significance, and the I^2 statistic. When we explored weight improvement in the MA versus placebo comparison, we obtained an I^2 of 66 %. We applied the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, which suggest that an I^2 value more than 60% may represent high heterogeneity (Deeks 2008). When we analysed data without the trials of Weisberg 2002; Yeh 2000 the I^2 became 2%. Those two trials with patients with COPD and geriatric cachexia could be quite different from the overall and could explain heterogeneity.

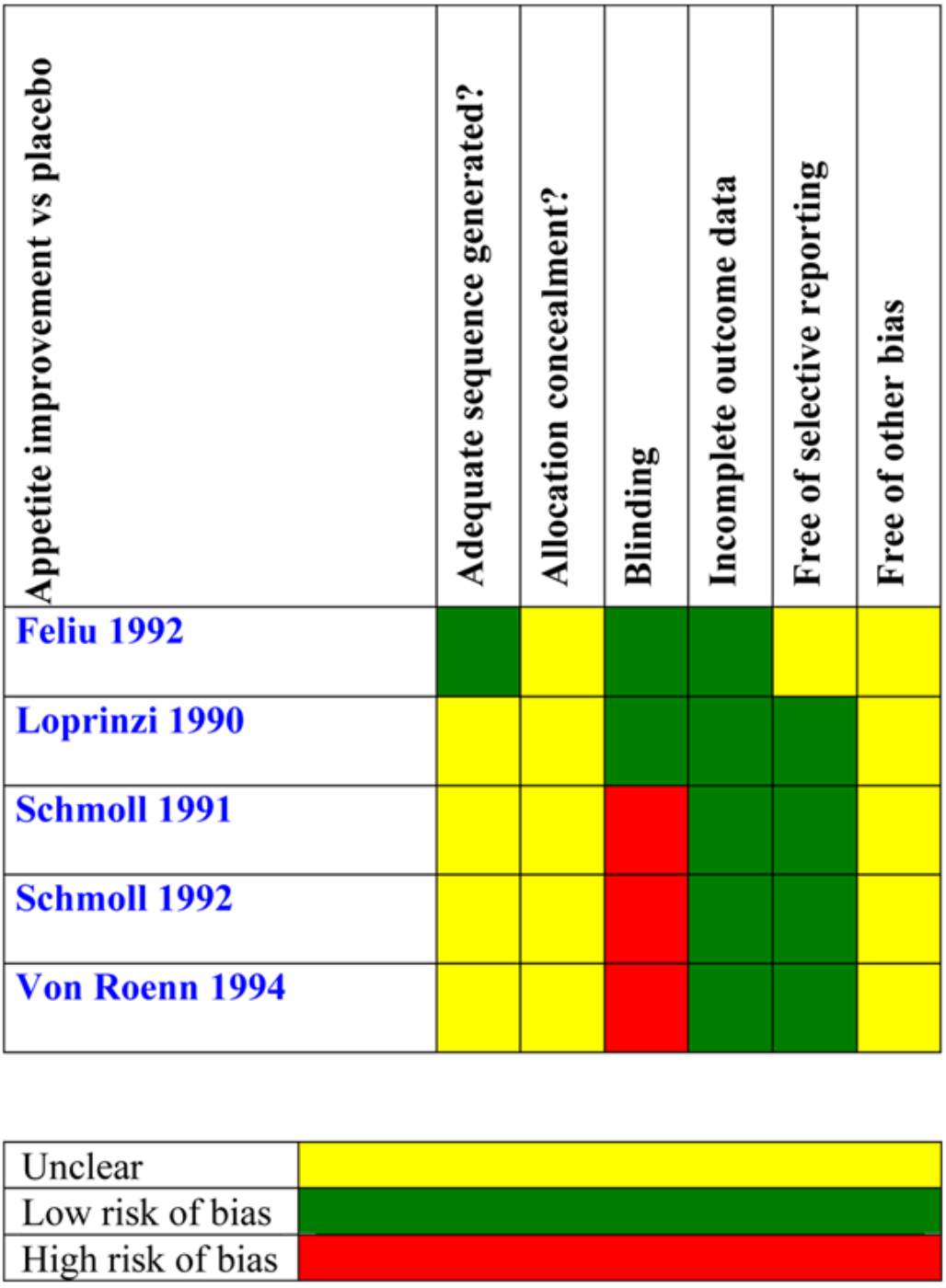
Quality of life

The overall results show improvement in quality of life for patients treated with MA (RR 1.78, 95% CI 1.09 to 2.92) (Analysis 1.5). The overall results for the cancer and AIDS patients subcategories were RR 1.91 (95% CI 1.02 to 3.59) and RR 1.49 (95% CI 0.47 to 4.69), respectively (Analysis 1.5). However, quality of life as a continuous variable shows no improvement (SMD 0.50, 95% CI -0.13 to 1.13) (Analysis 1.6).

Appetite

The overall results show appetite improvement for patients treated with MA (RR 2.19, 95% confidence interval (CI) 1.41 to 3.40)) (Analysis 1.1). The only subcategory that could be analysed was cancer patients and appetite improvement was detected (RR 2.57, 95% CI 1.48 to 4.49). We could not analyse the subcategories of AIDS patients and patients with other underlying pathologies because there was only one trial including AIDS patients. The quality of trials for this outcome is shown in Figure 4.

Figure 4.



For appetite gain, we did not find trials with patients with cancer or AIDS and only one subcategory could be analysed. There were patients with other underlying pathologies, namely chronic obstructive pulmonary disease (COPD) and geriatric cachexia (Herrejon 2011; Yeh 2000). The overall results show an

improvement for patients treated with MA (SMD 0.91, 95% CI 0.43 to 1.39) (Analysis 1.2)

Anthropometric values

Seven studies showed results for triceps skinfold thickness (TST). Only four of them had results which were statistically significant (Herrejon 2011; Vadell 1998; Von Roenn 1994; Weisberg 2002) and three did not show statistical significance (Beller 1997; Fietkau 1996; Tchekmedyian 1992;)

Two studies showed results for mid-arm circumference (MAC). Only one had results which were statistically significant (Eubanks 2002) and (Tchekmedyian 1992)did not show statistical significance.

In Beller 1997 the average difference in TST in mm between baseline and subsequent weeks was -0.28, -0.70 and +0.15 (P = 0.72) for placebo, lower doses of MA and higher doses of MA, respectively.

In Eubanks 2002 TST and MAC measurements were also increased compared with baseline for the entire MA-treated group at two, three and six months (P < 0.001 at all time points).

In Fietkau 1996, “There was no decrease or even a slight increase in the thickness of the triceps skinfold in MA group compared with a continuous decrease in the control group" and "No differences in upper arm muscle circumferences were observed between the groups”.

In Herrejon 2011 the mean differences in TST at eight weeks were 0.8 versus -0.1 (P = 0.003) for the MA and placebo group, respectively.

In Vadell 1998 a significant increase in TST was noted in patients receiving higher doses of MA after the second month of treatment.

In Von Roenn 1994a “MA treatment presented the decrease of TST in patients receiving placebo and resulted in an increase in all doses tested”.

In Weisberg 2002 the mean TST values in the MA group increased significantly when compared to the placebo group: 1.35 ± 2.38 (n = 72) versus 0.13 ± 2.24 (n = 73). Only Weisberg’s trial described mean difference and standard deviation (SD)

In Tchekmedyian 1992 there were no significant changes in MAC or TST in either group at one month.

Megestrol acetate versus other drugs

We found seven trials in this group: Loprinzi 1999a; Loprinzi 1999b; Jatoi 2002; Jatoi 2004 in the subcategory of cancer and Batterham 2001; Mwamburi 2004; Summerbell 1992; Timpone 1997 in the subcategory of AIDS. Loprinzi 1999 (Loprinzi 1999a; Loprinzi 1999b) compared MA to fluoxymesterone and dexamethasone, respectively. The analysis of Loprinzi 1999 was carried out by dividing the total number of placebo patients by two. In other words, the number of placebo patients in each comparison was taken to be 79 instead of 158

Weight gain

The overall results show weight improvement (RR 1.66, 95% CI 1.09 to 2.52) (Analysis 2.3). Three studies in the subcategory of cancer patients (Jatoi 2002; Jatoi 2004; Loprinzi 1999a; Loprinzi 1999b) and two in the subcategory of AIDS patients (Mwamburi 2004; Summerbell 1992) were considered.

The overall results for the outcome weight gain show improvement (MD 2.50, 95% CI 0.37 to 4.64) (Analysis 2.4). However, the overall results for each subcategory show no weight gain either in cancer or in AIDS patients (MD 0.61, 95% CI -0.15 to 1.38 and MD 4.85, 95% CI -0.79 to 10.49, respectively) (Analysis 2.4).

Quality of life

Two trials (Jatoi 2002; Loprinzi 1999a) included in the analysis measured health-related quality of life as an outcome using different instruments. Quality of life did not show any benefit (RR 1.05, 95% CI 0.77 to 1.44 and SMD 0.20, 95% CI -0.02 to 0.43, respectively).

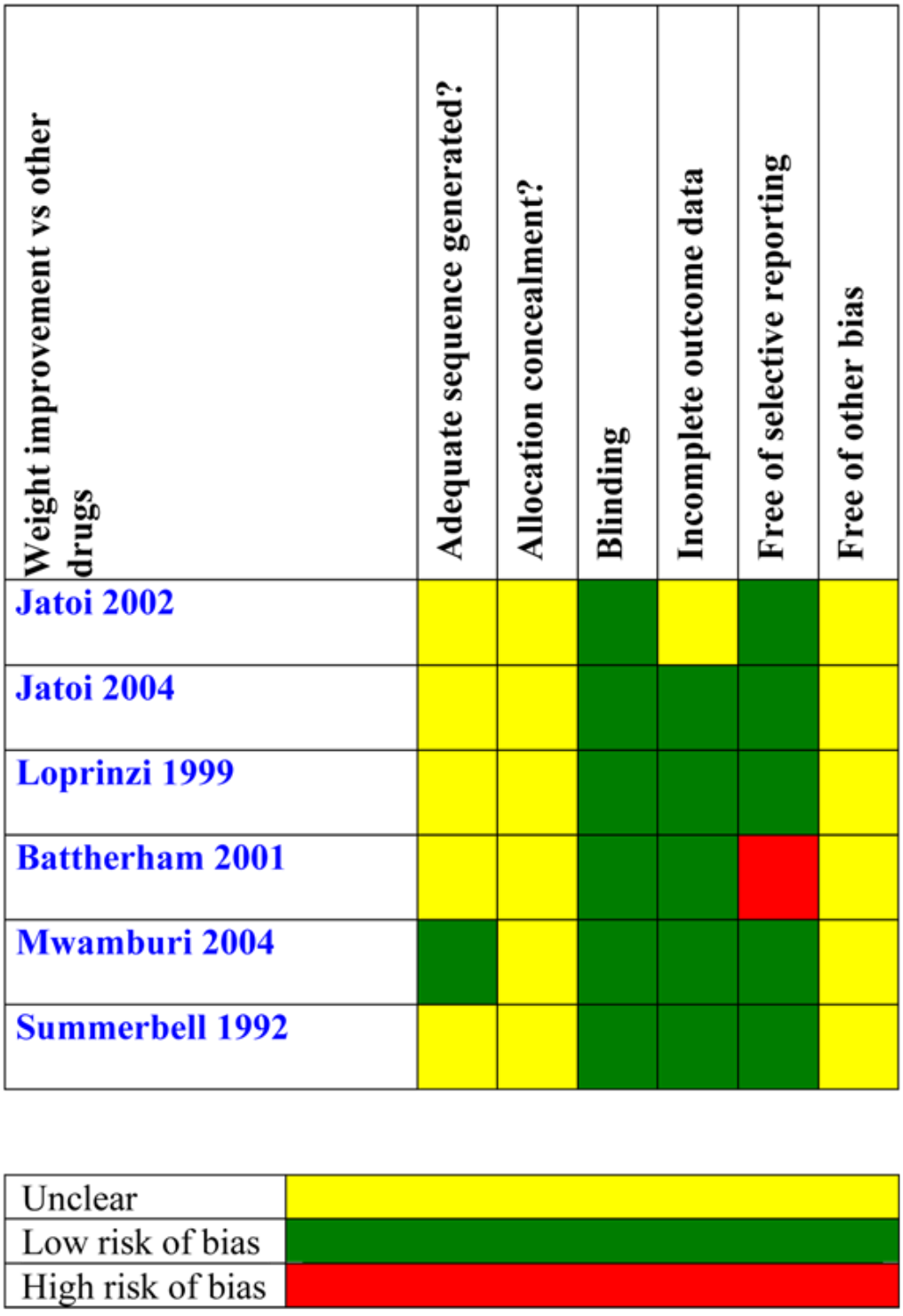
Appetite

When we looked at the overall results, MA did not show benefits in terms of appetite improvement in comparison with other drugs in any category (RR 1.03, 95% CI 0.64 to 1.67) (Analysis 2.1). The only trial available in this analysis was Loprinzi 1999.

Appetite gain as a continuous variable could only be analysed in one trial (Batterham 2001) and shows lack of efficacy (MD 1.60, 95% CI -1.28 to 4.48) (Analysis 2.2).

The quality of trials for the outcomes appetite and weight improvement is shown in Figure 3 and Figure 5.

Figure 5.



Anthropometric values

In Macbeth 1994 there was no evidence of statistical significance in the median change in TST at 12 weeks in either group.

Different dose levels of megestrol acetate

We analysed low doses versus high doses of megestrol. However, the definitions of low dose and high dose were according to those

used in each trial. Accordingly, in some trials (such as Beller 1997) low doses of MA were described as 160 mg and high doses as 480 mg; while in Wanke 2007 low doses were defined as 575 mg and high doses as 800 mg.

Weight gain

The overall results show weight improvement with high doses versus low doses (RR 0.77, 95% CI 0.64 to 0.93) (Gebbia 1996; Heckmayr 1992; Loprinzi 1994; Sancho-Cuesta 1993; Schmoll 1992; Ulutin 2002) (Analysis 3.2). All these trials were in the subcategory of cancer patients. When we analysed 160 mg of MA versus higher doses, the results remained unchanged, i.e. higher doses showed weight improvement (RR 0.72, 95% CI 0.52 to 0.99) (Analysis 3.3).

Only two trials were found for the outcome weight gain as a continuous variable and demonstrated no statistical significance (MD -0.94, 95% CI -3.33 to 1.45); both were in the subcategory of AIDS patients (Analysis 3.4).

Quality of life

Two studies included in this analysis (Von Roenn 1994; Wanke 2007) measured health-related quality of life as an outcome using different instruments. Quality of life did not show any benefit related to dose (RR 0.81, 95% CI 0.58 to 1.11and SMD 0.26, 95% CI -0.23 to 0.76) (Analysis 3.5; Analysis 3.6).

Appetite

The overall results show no differences in appetite improvement between doses (high and low doses) (Gebbia 1996; Schmoll 1992; Ulutin 2002). All trials were in the subcategory of cancer patients.

Anthropometric values

In Wanke 2007 there were no significant changes in TST or MAC in either group.

Safety

More than 40 adverse events were studied, categorised into more and less than 800 mg of MA.

Fifteen trials reported 'any adverse events' and show an increase in the risk of suffering some of them, independent of dose (RR 1.20, 95% CI 1.07 to 1.36) (Analysis 4.3). All studies except Jatoi 2002 are shown in the forest plot because this study had more 'any adverse events' in both arms than there were patients: 186/159 and 155/152 in the MA and placebo arm respectively. Therefore, 458 'any adverse events' were detected in 830 patients in the MA arm and 358 in 722 patients in the control arm. However, the overall results were the same.

The numbers of serious adverse events (SAE) were reported in four trials, but without further information. In these cases, SAEs seemed not to be related to MA (RR 2.10, 95% CI 0.98 to 4.47) (Analysis 4.2). Lower doses seemed to produce more SAEs (RR 4.65, 95% CI 1.33 to 16.29).

Dyspnoea was reported in eight trials and was related to MA (RR 2.23, 95% CI 1.01 to 4.93) (Analysis 4.11). Lower doses seemed to produce more dyspnoea (RR 2.80, 95% CI 1.02 to 7.67).

Deaths were reported in 11 trials and MA seemed to produce more deaths (RR 1.42, 95% CI 1.04 to 1.94) (Analysis 4.13). Higher doses seemed to produce more deaths (RR 1.66, 95% CI 1.08 to 2.57).

Oedema was reported in 15 trials and could be related to MA (RR 1.36, 95% CI 1.07 to 1.72) (Analysis 4.31). Higher doses seemed to produce more oedema (RR 1.37, 95% CI 1.04 to 1.81).

Impotence was reported in 13 trials and MA produced more impotence than placebo or other drugs (RR 2.58, 95% CI 1.78 to 3.75) (Analysis 4.24). Both lower and higher doses were related to this adverse event (RR 2.89, 95% CI 1.33 to 6.26 and RR 2.49, 95% CI 1.63 to 3.81, respectively).

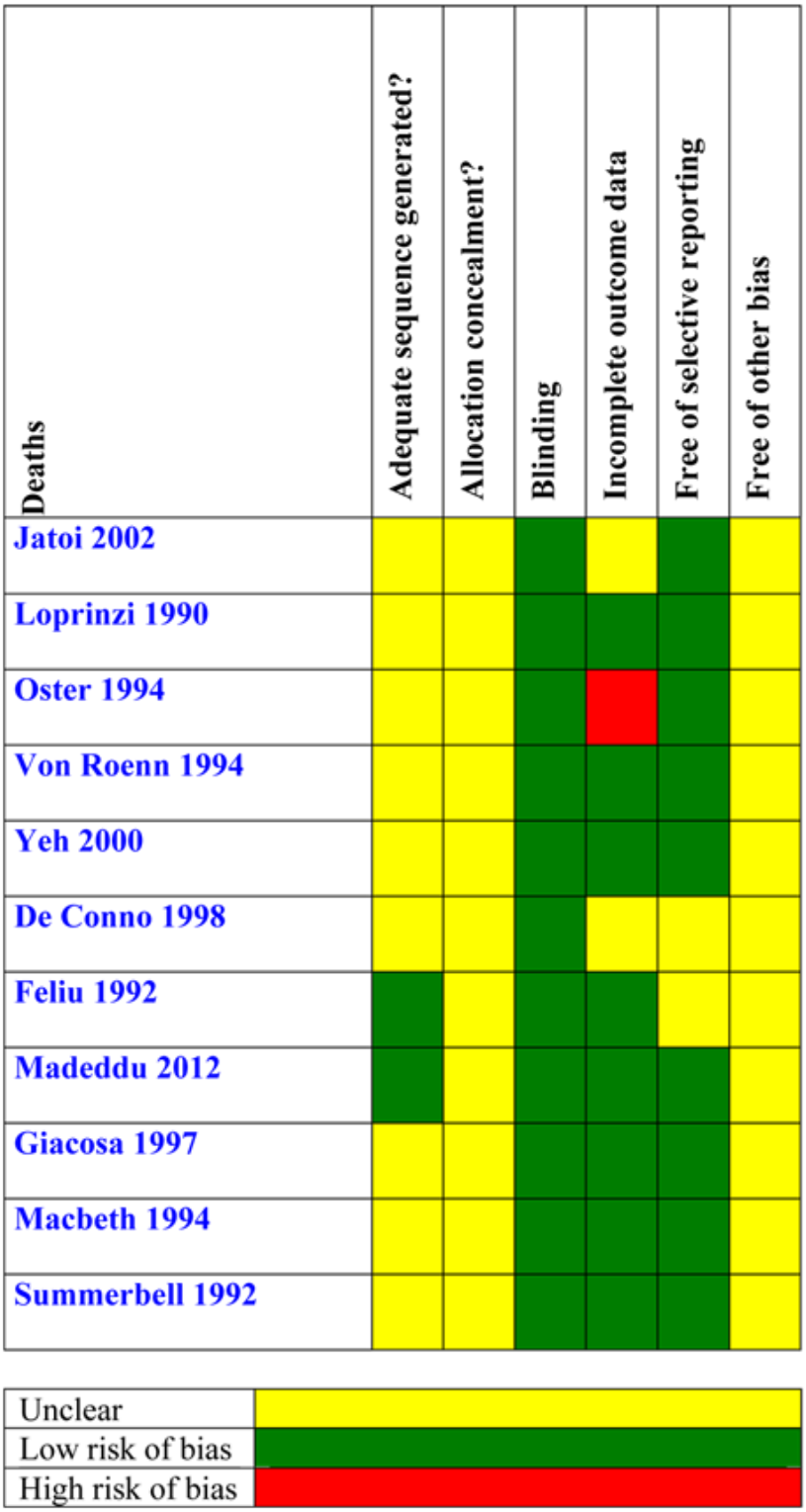
Nausea and vomiting were reported in 12 trials and MA produced less nausea and vomiting (RR 0.58, 95% CI 0.45 to 0.74) (Analysis 4.29). Both lower and higher doses were related to this adverse event (RR 0.51, 95% CI 0.37 to 0.72 and RR 0.68, 95% CI 0.46 to 1.00, respectively).

Thromboembolic phenomena including thrombophlebitis were reported in 11 trials and MA produced an overall increased risk (RR 1.84, 95% CI 1.07 to 3.18) (Analysis 4.42). However, neither higher doses nor lower doses showed statistical significance (RR 2.35, 95% CI 0.93 to 5.94 and RR 1.62, 95% CI 0.82 to 3.18, respectively).

Sixteen trials described withdrawals (RR 0.94, 95% CI 0.83 to 1.06) (Analysis 4.44). Neither higher doses nor low doses showed statistical significance in the MA group versus the placebo group (RR 0.92, 95% CI 0.80 to 1.06 and RR 0.98, 95% CI 0.75 to 1.28, respectively).

The quality of trials for the outcome of death is shown in Figure 6.

Figure 6.



Sensitivity analysis

This 2013 update of the review does not show any change with regard to the sensitivity analyses from the previous review (2006).

We undertook sensitivity analysis with trials where patients received more than 12 weeks of MA versus any drugs or placebo for any condition (cancer patients, AIDS, other underlying pathology).

We analysed three outcomes: appetite improvement, weight improvement and weight gain.

One trial studied appetite at six weeks and did not show an increase in appetite compared to more than six weeks (Analysis 5.1). Appetite did not change with treatment for less or more than 12 weeks (RR 1.80, 95% CI 1.06 to 3.04 and RR 1.56, 95% CI 1.13 to 2.16, respectively) (Analysis 5.2).

No differences were shown for weight improvement with less or more than 12 weeks of treatment (RR 1.40, 95% CI 0.90 to 2.18 and RR 1.46, 95% CI 0.92 to 2.31, respectively) (Analysis 5.6).

Weight gain was related to treatment duration of less of 12 weeks, but not to more than 12 weeks (MD 1.96 , 95% CI 1.06 to 2.87 and MD 1.94, 95% CI -1.64 to 5.53, respectively) (Analysis 5.8).

Although appetite is a subjective perception and could be related to blinding, we did not detect this association; on the contrary, we found that only blinded trials showed an increase in appetite (RR 1.96, 95% CI 1.17 to 3.27 and RR 1.53, 95% CI 0.82 to 2.87 for blinded and open-label trials, respectively) (Analysis 5.9).

Weight improvement only showed benefit in blinded trials (RR 1.63, 95% CI 1.15 to 2.32 and RR 1.14, 95% CI 0.53 to 2.47 for blinded and open-label trials, respectively) (Analysis 5.11).

We also analysed according to a more broad definition of quality, using the Jadad scale of high quality (3 to 5 points) or low quality (0 to 2 points). Appetite was not related to quality (high quality RR 2.31, 95% CI 0.93 to 5.72 and low quality RR 1.47, 95% CI 0.96 to 2.27) (Analysis 5.13). Weight improvement was not related to quality (high quality RR 1.50, 95% CI 1.07 to 2.10 and low quality RR 1.60, 95% CI 1.17 to 2.20) (Analysis 5.14). When we analysed weight gain according to quality, both the categories of high and low quality were favourable to MA (MD 1.90, 95% CI 0.89 to 2.91 and MD 2.30, 95% CI 0.25 to 4.35) (Analysis 5.15).

We also analysed whether the number of patients in the trials could be related to results for the main outcomes. We analysed two groups with more and fewer than 100 patients. Neither appetite nor weight improvement were related (Analysis 5.19 and Analysis 5.12, respectively). However, weight gain in studies with fewer than 100 patients showed a MD of 3.45 (95% CI 0.82 to 6.08) and a MD of 1.13 (95% CI 0.59 to 1.68) with more than 100 patients (Analysis 5.20). Consequently, small trial size may be related to weight gain.

We explored the duration of trials with oedema as an adverse event. This seemed to be related to trials of shorter duration: one to four weeks (RR 1.81, 95% CI 1.07 to 3.08), five to eight weeks (RR 1.43, 95% CI 1.04 to 1.97) versus 9 to 12 weeks (RR 1.10, 95% CI 0.82 to 1.46) (Analysis 5.16). When we explored trials with thromboembolic phenomena the shortest trials, with less than 12 weeks of follow-up, showed a RR of 2.59(95% CI 1.16 to 5.76) whereas trials with follow-up of 12 or more weeks did not show statistical significance (RR 1.45, 95% CI 0.71 to 2.94) (Analysis 5.17).

We carried out two sensitivity analyses to study death. In the first one, we explored duration of exposure to MA and this suggested a link (Analysis 5.25). When deaths and pathology were explored, the association was not significant, but cancer and AIDS patients were more likely to suffer death as an adverse event (Analysis 5.26). The explanation could be thromboembolic phenomena, although pulmonary embolism was not detected in the trials (only two trials reported this). It is known that pulmonary embolism is frequently unreported in 'real life'. We need to emphasise that the mortality results are sensitive to the trial of Jatoi 2002, so this result needs to be interpreted with caution.

DISCUSSION

Summary of main results

The aim of the present update of the review was to assess the efficacy, effectiveness and safety of megestrol acetate (MA) for the management of anorexia-cachexia syndrome, a common clinical problem that substantially impacts upon the quality of life and survival of affected patients.

Our search strategy allowed us to identify all relevant studies. We tried to include more data by requesting this from authors but unfortunately very few new data were introduced in this update.

Our systematic review suggests that patients with cachexia-anorexia syndrome treated with MA improve their weight and appetite (mean difference (MD) for weight gain 1.96 kg (95% confidence interval (CI) 1.11 kg to 2.81 kg) (Analysis 5.15); risk ratio (RR) for appetite improvement for any condition at six or more weeks of follow-up 1.70 (95% CI 1.14 to 2.54) (Analysis 5.1)). This overall result was obtained from trials with a duration of 14 to 180 days. Most of the trials had a follow-up of around 56 to 84 days.

Appetite and weight improvement was seen in the subcategories of cancer and AIDS patients when comparing MA with placebo. When MA was compared with other drugs, weight improvement was only seen in cancer patients. Quality of life improvement was seen in both subcategories of cancer and AIDS, when comparing MA-treated patients with placebo, but not against other drugs. However, no clear benefits were detected for quality of life gain (standardised mean difference (SMD) 0.32, 95% CI -0.02 to 0.65).

More adverse events were related to MA than placebo ('any adverse event') (RR 1.20, 95% CI 1.07 to 1.36). Serious adverse events were related to lower doses (< 800 mg/day RR 4.65, 95% CI 1.33 to 16.29). Dyspnoea seemed to be related to lower doses of MA (RR 2.23, 95% CI 1.01 to 4.93). Oedema and thromboembolic phenomena were common adverse events (RR 1.36, 95% CI 1.07 to 1.72 and RR 1.91, 95% CI 1.13 to 3.23, respectively). Deaths seemed to be increased (RR 1.43, 95% CI 1.05 to 1.96), especially with higher doses (RR 1.66, 95% CI 1.08 to 2.57). We could not pool data for anthropometrics values, but all results from the included trials are shown in Effects of interventions.

Overall completeness and applicability of evidence

All the planned outcomes have been analysed. Unfortunately, a large proportion of data available in the included trials could not be pooled because the authors did not provide enough information or data were not complete. This review has focused on the patients that were selected in the initial design of the review. Cancer and AIDS patients were the most common disease categories; the elderly and patients with chronic obstructive pulmonary disease (COPD) were new subcategories included in this review.

The mortality associated with cachexia-anorexia syndrome was high and the review failed to show any improvement with MA; in fact mortality was increased. This conclusion should be taken with caution, however, because the severity of illness in these patients

is high and they have a high risk of death. Increased death was related only to higher doses in all trials except Yeh 2000. It must also be stressed that these results are sensitive to the removal of the trial with most weight (Jatoi 2002) (RR 2.69, 95% CI 0.93 to 7.78), so must be taken with caution. However, none of the trials included in the review were designed to investigate mortality as primary endpoint and duration of follow-up was very short in most, so this unexpected result requires serious additional research in the form of clinical trials with longer follow-up and survival as a main outcome.

Most trials defined weight loss as a loss of more than 5% of previous weight. Appetite and weight gain showed benefits, however, in most of the trials this weight gain did not result in the recovery of the initial weight. In particular, the benefits of weight gain compared with placebo were in the range of 2 kg. The likelihood of oedema and thromboembolic phenomena means that patients should be informed of these adverse events.

The included trials did not have long-term follow-up. Since MA can be prescribed for several months in the treatment of cachexia-anorexia syndrome, adverse events could be more relevant than those described in the present review.

Quality of the evidence

The main results are shown in Summary of findings for the main comparison and we rated the quality from low to high using the GRADE system. We have calculated numbers needed to treat for an additional beneficial outcome (NNTB) from the risk ratio according to the formula NNT or NNH = 1/ACR*(1-RR), where ACR = assumed control risk and RR = risk ratio.

1. Appetite improvement versus placebo (Figure 4). There is an improvement in appetite but the quality of the evidence is downgraded to **very low** because the risk bias for sequence generation was low only in Feliu 1992. Moreover, allocation concealment was unclear in all trials and in three out of five trials we rated the outcome appetite as high risk of bias because it could be sensitive to lack of blinding. The statistical test for heterogeneity was moderate (P < 0.04 and I^2 = 59%; NNTB = 4, 95% CI 2 to 11). Doses of MA compared with placebo were very different, ranging from 160 mg to 960 mg in each subgroup.
2. Weight improvement versus placebo (Figure 3). We rated eight out of 10 trials as unclear regarding adequate sequence generation; we rated only one trial as low risk for allocation concealment. We rated all studies as low risk of bias for blinding. We rated Schmoll 1991; Schmoll 1992 and Von Roenn 1994 as low risk because lack of blinding is not related to weight. We rated only one study as high risk of bias due to incomplete outcome data addressed. We rated all trials as unclear with respect to 'other bias'. The results were quite similar and CI values overlapped for most of the trials. However, two studies (Feliu 1992; Schmoll 1991) showed higher effects and the CI was quite wide. The statistical test for heterogeneity was moderate (P = 0.02 and I^2 = 53%). The quality of the evidence is **very low** and the NNTB = 12 (95% CI 6 to 69).
3. Appetite improvement versus other drugs (Figure not shown). Only one trial showed improvement but there was an unclear risk of bias for sequence generation and allocation concealment and a high risk of bias for blinding. The quality of the evidence was low and the NNTB was not statistically significant.
4. Weight improvement versus other drugs (Figure 5). We rated all studies except Mwamburi 2004 as unclear risk of bias for adequate sequence generation and allocation concealment. The statistical test for heterogeneity was moderate (P = 0.05 and I^2 = 51%). The CI values overlapped for most of the studies. Cancer patients showed a better response in terms of weight. The quality of the evidence was **very low** and the NNTB = 22 (95% CI 9 to 159).
5. Deaths (Figure 6). We rated only two trials out of 11 as low risk of bias for adequate sequence generation and blinding. Allocation concealment was unclear in all trials. The CI values did not overlap. There was no large variation in the effect. The statistical test for heterogeneity was low (P < 0.05 and I^2 = 0%). Follow-up for this outcome was very short (up to 15 weeks) and we cannot disregard the possibility that in 'real life' very sick patients taking MA for a longer time, the number of deaths could increase. The quality of the evidence was **very low** and the number needed to treat for an additional harmful outcome (NNTH) = 23 (95% CI 10 to 200).
6. Thromboembolic phenomena (Figure not shown). We rated adequate sequence generation as low risk in three out of 10 trials, and rated allocation concealment as low risk only in two out of 10 trials. The statistical test for heterogeneity was low (P < 0.9 and I^2 = 0%). Thrombosis is a common complication in cancer patients and venous thromboembolism (VTE) is found at autopsy in at least 50% of cancer patients (Thompson 1952). However, assessment of the true incidence of VTE in cancer patients is difficult because most of these patients receive chemotherapy or hormonal therapy which could precipitate VTE. In addition, many cancer patients have indwelling central venous lines, which can also initiate thrombotic events in relation to the catheter (Verso 2003). Consequently, we have calculated the NNTH assuming different basal risks from those obtained in the trials, namely 0.02, 0.10 and 0.50 in cancer patients. The resulting NNTH values were NNTH = 55 (95% CI 22 to 385), NNTH = 11 (95% CI 4 to 77) and NNTH = 2 (95% CI 1 to 15), respectively. The quality of the evidence was **very low**.
7. Oedema (Figure not shown). We rated only three out of 11 trials as low risk regarding adequate sequence generation. We rated only two out of 11 trials as low risk for allocation concealment. We rated incomplete outcome data as low risk in eight out of 11 trials. The statistical test for heterogeneity was low (P = 0.76 and I^2 = 0%). The quality of the evidence was rated as **very low** (NNTH = 28, 95% CI 4 to 143).

Potential biases in the review process

We have estimated that the potential bias in this review is low. Objectivity during the review process cannot be assessed, but the evaluation of trials to be included was done in pairs. We detected one trial that was unpublished due to early stopping because of increased mortality. Despite the fact that this trial was removed, mortality remained unchanged. We created funnels plot for all outcomes with more than 10 trials and these did not suggest publication bias. (These figures are not shown). The authors of this review do not have any conflicts of interest regarding MA.

Agreements and disagreements with other studies or reviews

Previous systematic reviews have shown similar results despite the fact that they did not include the same trials. Ruiz-Garcia 2002

found weight gain (MD 0.448 kg, CI 95% 0.02 to 0.87) only with low MA doses (≤ 240 mg). Pascual 2004 concluded that MA improved appetite (RR 2.31, 95% CI 1.52 to 3.59), led to weight gain (RR 1.88, 95% CI 1.43 to 2.47) and improved health-related quality of life (RR 1.52, 95% CI 1.00 to 2.30). Lesniak 2008 concluded, as in the present review, that MA increases appetite (RR 3.00, 95% CI 1.86 to 4.84, NNT = 3) and leads to weight gain (RR 1.71, 95% CI 1.24 to 2.36, NNT = 8). None of the reviews mentioned showed an increase in mortality in MA arm. Additionally, they either did not explicitly analyse adverse events or did not include them in their protocols.

In palliative medicine, quality of life means not only the control of physical symptoms, functioning in daily life and psychological and social well being; quality of life also implies care of the patient's spiritual and existential concerns and also the perception by members of the patient's family of the quality of their care. It is our opinion that improving appetite and slight weight gain is not enough to improve quality of life in these patients.

Prevalence of cachexia in AIDS patients is high (from 18% to 38% in cohort studies) despite antiretroviral therapy (Campa 2005; Tang 2005). The prevalence of weight loss and wasting has not changed over time; it is as frequent now as it was in 1997 (Tang 2005). The conclusion of the present review is in line with the statement of Mangili 2006, "Although there has been the presumption that, if weight loss is associated with morbidity and mortality in HIV infection, then improvements in weight would lead to improved QoL, there has been little data that support this". The conclusions of this review regarding geriatric patients are in line with the guidelines of the American Geriatrics Society (Fick 2012) which state "Rationale: minimal effect on weight; increases risk of thrombotic events and possibly risk of death in older.. Recomendation: Avoid; Quality of evidence: moderate; Strenght of recommendation: Strong".

AUTHORS' CONCLUSIONS

Implications for practice

The new trials identified and included in the present review update have not led to significant changes to the conclusions of the previous review (megestrol acetate (MA) improves appetite and slightly increases weight, without clinical relevance), except for adverse events. MA may be prescribed in patients with cancer to increase appetite and improve weight gain. Currently, there is no evidence to recommend MA to improve quality of life. This update has followed The Cochrane Collaboration guidelines for an unbiased review. Quality is difficult to define, since it depends on the design, conduct and analysis of a trial, its clinical relevance or the quality of reporting. Studies of low methodological quality can alter the interpretation of the benefit of an intervention. In this update, we assessed 58% of the trials as high quality for some outcomes such as improvement of weight.

Many concerns remain unresolved. Health-related quality of life is an important goal in health care and cancer clinical trials, and is the cornerstone for delivery of good palliative medicine. The increasing recognition of patient autonomy means that subjective measures will become more important and, in the current climate of evidence-based medicine, such measures must be valid and reliable.

Despite MA being approved US Food and Drug Administration for use in AIDS patients, this drug failed to show weight improvement and weight gain when compared with other drugs. MA compared with placebo was effective in AIDS patients in one trial.

In summary, MA could be prescribed to improve appetite in the context of palliative medicine, but it should be emphasised that this drug will probably not lead to full weight loss recovery or improve quality of life, and it is related to adverse events, including an increased risk of death.

Implications for research

This update of the review shows that there is still a need for high-quality trials focused on the evaluation of the effectiveness of MA. Trials with long-term follow-up are needed to rule out an increase in mortality. Even though the US Food and Drug Administration has approved MA for use in AIDS patients, more research is needed in this respect.

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Previous review

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Present review

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Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;**266**:93-8.

References to other published versions of this review

Berenstein G 2005

Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858]

Berenstein G 2011

Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Batterham 2001

Methods	Randomised controlled in a tertiary referral hospital, Sydney
Participants	15 HIV pts a) 4 M Mean age 46 yrs b) 8 M Mean age 44 yrs c) 5 M Mean age 42 yrs 5 completed and then randomised 3 to nandrolone and 2 to megestrol
Interventions	a) MA 400 mg/d orally b) Nandrolone decanoate 100 mg/fortnight as an intramuscular injection c) Dietary counselling

Batterham 2001 *(Continued)*

	Duration 12 weeks
Outcomes	Weight and height Appetite VAS 10-point score 0 = poor appetite 10 = good appetite Dietary intake %
Notes	12 weeks of treatment QS = 2 Cachexia was defined as unintentional weight loss of at least 5% of their usual body weight despite an adequate nutritional intake (> 85% estimated requirements calculated using the Harris Benedict equation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were similar in all groups
Selective reporting (reporting bias)	High risk	Yes. Authors reported only data at 12 weeks and not at 24 weeks
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Beller 1997

Methods	Double-blind, randomised, controlled, multicentre (15), stratified by institution and whether receiving any antitumour treatment
Participants	240 cancer pts a) 81 pts = 53 M + 28 F (9 pts = 50 yrs, 49 pts = 51 to 70 yrs, 23 pts = > 71 yrs) b) 80 pts = 52 M + 28 F

Beller 1997 *(Continued)*

	(7 pts = less than 50 yrs, 52 pts = 51 to 70 yrs, 21 pts = > 70 yrs) c) 79 pts = 54 M + 25 F (12 pts = 50 yrs, 51 pts = 51 to 70 yrs, 16 pts = > 70 yrs) Patients were excluded if they were under 18 years of age, had physical or functional obstruction to food intake or impaired digestive/absorptive function, were pregnant, were receiving concurrent corticosteroid treatment, were unable to complete quality of life forms, had endocrine-sensitive malignant disease (i.e. of breast, prostate, uterus), had a life expectancy of less than 2 months, or were diabetic
Interventions	a) MA 480 mg/d orally b) MA 160 mg/d c) Placebo
Outcomes	QoL 5 linear analogue self assessment scales (LASA) asked patients about 5 factors: physical well being, mood, pain, nausea and vomiting, and appetite, LASA uni scale of overall QoL and the Spitzer QoL Index, completed by the clinician Appetite (LASA score) Nutritional status Weight Triceps skinfold Mid-arm circumference
Notes	2 weeks of treatment QS = 3 Cachexia was defined as a body weight at least 5% below ideal, or unintentional loss of at least 5% of usual body weight, and eligible for the study. Withdrawals from randomised treatment (other than death whilst still on treatment) included drug intolerance or toxicity in 28 cases, deterioration in patient's condition not attributed to study treatment in 36 cases, and refusal by patient to continue in the study in 18 cases. “The proportion of incomplete data and withdrawals from treatment was very similar for the three treatment groups”.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Low risk	By telephone through a central office
Blinding (performance bias and detection bias) All outcomes	Low risk	No data about blinding but unlikely the outcome could be influenced by lack of blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No data about blinding but unlikely the outcome could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No data about blinding but unlikely the outcome could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups

Beller 1997 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk. No information in the meta register of clinical trials or http://apps.who.int/trialsearch
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Casado 2008

Methods	Randomised controlled trial, not blinded
Participants	94 patients with non hormone-sensitive cancer
Interventions	MA tablets 160 mg MA tablets 960 mg Placebo At least 12 weeks
Outcomes	Weight QoL, appetite
Notes	Cachexia was defined as weight loss of < 5% of ideal weight QS: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random tables
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcome was weight
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were balanced, most for progression of cancer (no data between groups); patients deciding stop treatment = 5 (no data between groups) and related to adverse effects of treatments
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported but data were shown in graphical manner or before/after, but not as mean change with SD in each group or as number of patients that gained appetite, weight or QoL, so only adverse events were included in the review

Casado 2008 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

De Conno 1998

Methods	Double-blind, randomised, controlled
Participants	42 patients with advanced non hormone-responsive tumours a) 21 pts = 15 M + 6 F Mean age 63 yrs b) 21 pts = 16 M + 5 F Mean age 58 yrs
Interventions	Phase A is a double-blind, placebo-controlled trial comparing MA 320 mg/day versus placebo for 2 weeks. In phase B all patients were treated with MA and the dosage was titrated according to clinical response for 76 days.
Outcomes	Appetite score (numeric scale ranging from 0 to 10), Karnofsky, weight, subjective food intake, pain intensity, patient's preference and quality of life (TIQ sub scales)
Notes	14 days of treatment QS = 3 Withdrawals in the Phase A were 4 in MA and 5 in placebo group. Cachexia was not defined but patients had a weight loss of > 10%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Unclear risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of low risk or high risk;
Blinding of outcome assessment (detection bias) All outcomes	High risk	Appetite is the main outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data have been imputed using appropriate methods
Selective reporting (reporting bias)	Unclear risk	All outcomes in the paper have been reported but we did not find this trial in the meta register of clinical trial or http://apps.who.int/trialsearch

De Conno 1998 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Eubanks 2002

Methods	Randomised, double-blind, placebo-controlled study
Participants	17 cystic fibrosis patients with growth failure, most < 18 years old a) 10 pts = 5 M + 4 F Ranging from age 6 to 18 yrs, 1 F 35 yrs b) 7 pts = 3 F + 4 M Ranging from age 6 to 15 yrs
Interventions	a) MA 10 mg/kg per day b) Placebo On day 0 of the study, patients were randomly assigned to receive either MA (n = 10) or placebo (n = 7) at a starting dose of 10 mg/kg per day. Medication doses were increased by 2.5 mg/kg per day for weight gain < 2% above baseline at day 30 or < 5% above baseline at days 60 or 90 (maximum dose, 15 mg/kg per day). Doses were decreased for weight gain > 5% above baseline at day 30 or > 10% above baseline at days 60 or 90. Medication doses were decreased by 2.5 mg/kg per day for side effects. At the conclusion of this study, the mean dose of MA was 7.5 mg/kg per day and the mean dose of placebo was 13.9 mg/kg per day.
Outcomes	Weight for age (WAZ) gain included both fat and fat-free mass Improved pulmonary function (forced vital capacity and forced expiratory volume in 1 second) and side effects
Notes	Growth failure defined as no weight gain in the preceding 6 months, per cent ideal body weight of < 85%, weight < 5th percentile for age, or weight for height < 5th percentile Follow-up was 180 days QS = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	“Through the use of a computer-generated randomisation schedule”
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Each subject received MA or a placebo of similar physical characteristics (provided by Bristol Meyers-Squibb, New York City, NY). Participants, treating physicians, and ancillary staff were blinded to the treatment group”.
Blinding of outcome assessment (detection bias)	Low risk	The main outcome is not likely to be influenced by blinding

Eubanks 2002 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients in the treatment group completed the study. 3 patients in the placebo group withdrew when they failed to observe a treatment effect
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Feliu 1992

Methods	Double-blind randomised controlled trial
Participants	150 cancer patients with cancer non hormone-dependent a) 76 pts = 58 M + 8 F Mean age 57 yrs b) 74 pts = 55 M + 7 F Mean age 58 yrs
Interventions	a) MA 240 mg/day b) Placebo
Outcomes	Body weight, appetite (described as changes in SSA score in 2 ranges: 0 to 5 and 6 to 10) Functional status (PS score described as 2 ranges: less than 60% and more than 60%)
Notes	2 months of treatment QS = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	They used computer random generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study medication was provided in blinded packages
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was body weight
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals; authors reported data for all patients that were alive

Feliu 1992 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported but we did not find this trial in the meta register of clinical trials or http://apps.who.int/trialsearch
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Fietkau 1996

Methods	Double-blind randomised controlled trial
Participants	64 cancer patients with head and neck cancer 61 pts: a) 31 pts = 25 M + 6 F Mean age 52 yrs b) 30 pts = 24 M + 6 F Mean age 48 yrs
Interventions	a) MA 160 mg/day b) Placebo During 6 weeks
Outcomes	Weight, anthropometric and biochemical parameters, and QoL (Padilla Index)
Notes	6 weeks of treatment during and up 6 weeks following radiotherapy Pts were stratified according oral feeding versus gastrostomy Definition of cachexia was weight loss of 5% over 6 weeks or 10% over the 6 months prior to radiotherapy Withdrawals were 1 in MA group and 2 more in placebo group QS = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome is not likely to be influenced by lack of blinding

Fietkau 1996 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient was withdrawn in each arm because of suspected side effects (diarrhoea, impotence respectively) and 1 patient in the placebo arm refused further participation following randomisation
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported and we did not find this trial in the meta register of clinical trials or http://apps.who.int/trialsearch
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Gambardella 1998

Methods	Double-blind randomised controlled
Participants	30 elderly cancer patients, 15 in each arm
Interventions	MA 320 mg daily versus placebo for 12 weeks
Outcomes	Weight, serum levels of interleukins and QoL
Notes	We found just 2 proceedings reporting this trial Cachexia was defined as weight loss < 6 kg in last 3 months Follow-up was 12 weeks No data about weight in placebo group QS: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Unclear risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The main outcome was body weight
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Gambardella 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Gebbia 1996

Methods	Randomised controlled trial
Participants	122 cancer pts a) 62 pts = 46 M + 16 F Mean age 63 yrs b) 60 pts = 42 M + 18 F Mean age 65 yrs
Interventions	a) MA 160 mg/d b) MA 320 mg/d
Outcomes	Appetite, body weight, pain, survival, Karnofsky Index
Notes	30 days of treatment QS = 2 Definition of cachexia was weight loss > 5%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	High risk	See below
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was a not blinded trial. One arm received 1 tablet and the other 2 tablets of MA
Blinding of outcome assessment (detection bias) All outcomes	High risk	The main outcome was appetite
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were quite similar and related to cancer: 1 patient died in the 160 mg/day arm and 2 patients died in the 320 mg/day arm at 30 days
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported but we did not find this trial in the meta register of clinical trials or http://apps.who.int/trialsearch

Gebbia 1996 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Giacosa 1997

Methods	Randomised controlled trial
Participants	28 patients with non hormone-sensitive cancer
Interventions	MA 320 mg/day plus standardised dietary counselling versus standardised dietary counselling (35 Kcal/day) 30 days of intervention
Outcomes	Body weight, appetite, daily food intake, body composition, psychological distress
Notes	Withdrawal: 10 patients were unevaluated due to early death (5 in each group) Cachexia was defined as weight loss > 10% of usual weight QS: 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not a blinded study but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not a blinded study but the outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were balanced but no data about 2 patients in the dietary counselling arm
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported but we did not find this trial in the meta register of clinical trial neither http://apps.who.int/trialsearch
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Heckmayr 1992

Methods	Randomised controlled trial
Participants	66 patients with advanced bronchogenic carcinomas a) 33 pts = 24 M + 9 F Mean age 65 yrs b) 33 pts = 27 M + 6 F Mean age 68 yrs
Interventions	a) MA 160 mg/daily b) MA 480 mg/daily
Outcomes	Weight Well being Appetite (subjective 10-point scale)
Notes	Treatment for 4 to 16 weeks Cachexia was defined as body weight loss > 10% QS = 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was not blinded but the main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was not blinded but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of any withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported but we did not find this trial in the meta register of clinical trials or http://apps.who.int/trialsearch
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Herrejon 2011

Methods	Randomised controlled trial, double-blinded
Participants	40 patients with stable COPD (without any exacerbation during the study)
Interventions	320 mg MA daily during 8 weeks versus placebo
Outcomes	Body weight, triceps skin fold thickness and analytic values
Notes	Cachexia was defined as body weight less > 5% QS: 5 NCT00507949

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Was external and warranted for the promotor Madaus
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The pills were similar and it was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Body weight
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 patients in each group were withdrawals
Selective reporting (reporting bias)	Low risk	NCT00507949; all outcomes that were planned were shown
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Jatoi 2002

Methods	Double-blind randomised controlled, multicentre (20)
Participants	469 cancer patients with cancer-associated anorexia other than brain, breast, ovarian or endometrial cancer a) 159 pts = 103 M + 56 F Mean age 65 yrs b)152 pts = 100 M + 52 F

Jatoi 2002 *(Continued)*

	Mean age 67 yrs c) 158 pts = 104 M + 54 F Mean age 67 yrs
Interventions	a) MA 800 mg/d liquid suspension +2 capsules placebo b) Dronabinol capsules 2.5 mg orally x + liquid placebo c) MA suspension 800 mg/d + dronabinol capsules 2.5 mg x 2
Outcomes	Appetite (validated questionnaires) Weight QoL Functional Assessment of Anorexia/Cachexia Therapy (FAACT) instrument uni scale and 13-item
Notes	Cachexia was defined as body weight loss > 5 pounds (2.3 kg) during the preceding 2 months QS = 4 Follow-up: as long as patients and healthcare providers thought it beneficial or until toxic side effects were shown. Follow-up median: 80 days (MA), 57 (DRO), 74 (MA+ DRO) (duration more than 4 weeks of treatment)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors used capsules and liquid placebo to assure the blinding in all groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The main outcome was appetite, without more details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were quite similar in all groups, but the number in each group was uncertain and only 45% of patients remained at the end of the first month
Selective reporting (reporting bias)	Low risk	All results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Jatoi 2004

Methods	Double-blind randomised controlled, multicentre (26)
Participants	421 cancer pts a) 140 pts = 97 M + 43 F

Jatoi 2004 *(Continued)*

	Mean age 65 yrs b) 141 pts = 104 M + 37 F Mean age 66 yrs c) 140 pts = 92 M + 48 F Mean age 66 yrs
Interventions	a) MA 600 mg/d liquid suspension + isocaloric, isonitrogenous placebo cans b) EPA supplement, 2 cans/d + placebo liquid suspension c) EPA supplement 2 cans/d plus MA liquid suspension 600 mg/d orally in combination
Outcomes	Weight Appetite (NCCTG questionnaire and FAACT) QoL (single-item uniscale)
Notes	Duration more than 3 months (patients continued treatment as long as both the patient and treating oncologist considered it beneficial or until concerning or intolerable side effects occurred) Cachexia was defined as a self reported, 2-month weight loss of at least 5 lb (2.3 kg) QS = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This double-dummy study design used an active EPA supplement and an identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No data about blinding but weight is unlikely to have been influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawals were balanced and well described
Selective reporting (reporting bias)	Low risk	All the outcomes were available and was registered
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Lesser 2006

Methods	Randomised clinical trial
Participants	Cancer patients with solid tumours and cachexia that were receiving chemotherapy

Lesser 2006 *(Continued)*

	74 pts accrued (72 eligible) Median age 64 yrs 42% females and 62% stage 4 disease 25 pts (arm 1: 8, arm 2: 17) completed 12 weeks of therapy and 20 remained in study
Interventions	The effects of oxandrolone and megestrol (no more details about doses) on weight, body composition and QoL in pts with solid tumours and weight loss receiving chemotherapy
Outcomes	Weight, body composition (main outcome) and QoL
Notes	Cachexia was defined as progressive weight loss on chemotherapy 12 weeks of follow-up QS: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Other bias	High risk	We have just a proceeding dated 2006. We have not found any paper with all the relevant data from this trial. There is a suspicion of publication bias.

Loprinzi 1990b

Methods	Double-blind randomised controlled trial
Participants	133 cancer pts (adults with advanced, incurable cancer - other than breast or endometrial cancer - who were experiencing anorexia, cachexia or both) a) 66 pts = 44 M + 23 F Mean age 69 yrs

Loprinzi 1990b *(Continued)*

	b) 67 pts = 44 M + 22 F Mean age 67 yrs
Interventions	a) MA 800 mg/d (5 tablets per day of 160 mg of MA) b) Placebo
Outcomes	Weight Appetite
Notes	1 month of treatment QS = 4 Cachexia defined as loss of body weight in the preceding 2 months of at least 5 lb Follow-up: median 1.6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors declared that placebo tablets were identical to MA and weight is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Weight is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients were moved from the study after randomisation but before the initiation of study (1 for additional treatment with prednisone and another due to a decline in physical condition), so all analyses were based on 133 eligible for treatment. 9 patients in each group had no weight recorded beyond their initial study weight and hence could not be included in analyses of weight. Withdrawals were balanced (nausea: 1 in MA and 1 in placebo group; refusal: 2 in MA and 4 in placebo group; physical deterioration: 1 in MA; inability to take oral medication: 2 in placebo).
Selective reporting (reporting bias)	Low risk	All the outcomes were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Loprinzi 1994

Methods	Randomised controlled trial

Loprinzi 1994 *(Continued)*

Participants	342 cancer pts a) 88 pts = 56 M + 32 F Mean age 67 yrs b) 86 pts = 54 M + 32 F Mean age 67 yrs c) 85 pts = 55 M + 30 F Mean age 67 yrs d) 83 pts = 54 M + 29 F Mean age 66 yrs
Interventions	a) MA 160 mg/d b) MA 480 mg/d c) MA 800 mg/d d) MA 1280 mg/d
Outcomes	Weight (primary outcome) Appetite, perceived food intake Serum albumin Toxicity
Notes	Median 66 days of treatment (9 weeks) QS = 1 Cachexia: the study required each patient to have lost at least 2.27 kg within the preceding 2 months or have an estimated daily caloric intake less than 20 kcal/kg Withdrawals low doses (160 + 480 mg/d of MA): 28 patients versus high doses (800 mg + 1280 mg/d of MA): 39 patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was not blinded but the main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was not blinded but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were balanced
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported

Loprinzi 1994 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Loprinzi 1999a

Methods	Randomised, controlled, multicentre study
Participants	475 cancer pts a) 79 pts = 55 M + 30 F Mean age 66 yrs b) 159 pts = 99 M + 60 F Mean age 66 yrs
Interventions	a) MA 800 mg/d b) Dexamethasone 3 mg/d 1 month of treatment The median durations of study for patients receiving MA, fluoxymesterone and dexamethasone were 64, 54 and 57 days
Outcomes	Appetite Weight QoL (uni scale)
Notes	QS = 2 Cachexia was defined as a history of losing at least 5 pounds within the previous 2 months (excluding perioperative weight loss) Quality of life, weight and body composition are assessed at baseline and monthly intervals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	High risk	See below
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not a blinded study and the outcome was appetite
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not a blinded study and the outcome was appetite
Incomplete outcome data (attrition bias) All outcomes	Low risk	After randomisation, 10 patients cancelled (before taking any study medication) and 11% were found to be ineligible, resulting in 475 assessable patients. For the effect of the study medications on patients' appetites, 311 (66%) of the

Loprinzi 1999a *(Continued)*

		patients completed a baseline questionnaire and at least 1 follow-up questionnaire. For the weight gain analyses, all patients with clinically apparent oedema or ascites were censored. Drop-out rates were quite similar: 71 patients in the MA group, 70 in the dexamethasone group and 70 patients in the fluoxymesterone group.
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Loprinzi 1999b

Methods	Randomised, controlled, multicentre study
Participants	475 cancer adult patients with advanced incurable cancer (other than breast, prostate, ovarian or endometrial cancer) a) 79 pts = 54 M + 29 F Mean age 66 yrs b) 158 pts = 100 M + 58 F Mean age 67 yrs
Interventions	a) MA 800 mg/d b) Fluoxymesterone 20 mg/d 1 month of treatment
Outcomes	Appetite Weight QoL (uni scale)
Notes	The median durations of study for patients receiving MA, fluoxymesterone and dexamethasone were 64, 54 and 57 days 1 month of treatment QS = 2 Cachexia was defined as a history of losing at least 5 pounds within the previous 2 months (excluding perioperative weight loss) Quality of life, weight and body composition are assessed at baseline and monthly intervals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	High risk	See below

Loprinzi 1999b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not a blinded study and the outcome was appetite
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not a blinded study and the outcome was appetite
Incomplete outcome data (attrition bias) All outcomes	Low risk	After randomisation, 10 patients cancelled (before taking any study medication) and 11% were found to be ineligible, resulting in 475 assessable patients. For the effect of the study medications on patients' appetites, 311 (66%) of the patients completed a baseline questionnaire and at least 1 follow-up questionnaire. For the weight gain analyses, all patients with clinically apparent oedema or ascites were censored. Drop-out rates were quite similar: 71 patients in the MA group, 70 in the dexamethasone group and 70 patients in the fluoxymesterone group.
Selective reporting (reporting bias)	Unclear risk	All outcomes in the paper have been reported
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Macbeth 1994

Methods	Randomised controlled trial, single-blinded
Participants	75 patients with advanced lung cancer
Interventions	38 patients received MA (460 mg/daily) and 37 patients received prednisolone (15 mg/day) for a minimum of 8 weeks Medication was suspended if the patient achieved their ideal weight
Outcomes	Weight, anorexia, quality of life
Notes	Withdrawals were 28 in the MA and 20 in the placebo group; the major cause was deaths: 14 in the MA group and 7 in the placebo Cachexia was defined as loss of > 5% of ideal body weight Trial was stopped at 12 weeks QS: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias)	Unclear risk	See below

Macbeth 1994 *(Continued)*

All outcomes		
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients were not blinded but: " an attempt was made to keep the clinicians unaware of which tablets the patients were taking…"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was not blinded but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were not balanced
Selective reporting (reporting bias)	Low risk	All the pre-specified outcomes were reported in private files
Other bias	High risk	The trial was stopped early for safety at 12 weeks

Madeddu 2012

Methods	Randomised Non-inferiority Open-label Single-centre
Participants	60 patients (56 evaluable) with cancer and a life expectancy ≥ 4 months 33 M/23 F Age (years) 62.6 ± 8.1 versus 66.3 ± 10.7 (MA group)
Interventions	a) Polyphenols + L-carnitine 4 G/day + celecoxib 300 mg/day b) Polyphenols + L-carnitine 4 G/day + celecoxib 300 mg/day + MA 320 mg/day Follow-up 16 weeks (4 months)
Outcomes	Primary: lean body weight, physical activity Secondary: grip strength, 6-minute walk test, fatigue, resting energy expenditure (REE), body weight, appetite by visual analogue scale, serum levels of IL-6 and TNF-a, plasma levels of C-reactive protein, quality of life (EORTC QLQ-C30) and Glasgow Prognostic Score Clinical: objective clinical response, progression-free survival (PFS) and overall survival (OS)
Notes	Cachexia loss > 5% ideal or pre illness weight 56 patients evaluable: 4 deaths, 2 in each group QS = 2

Risk of bias

Bias	Authors' judgement	Support for judgement

Madeddu 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding or incomplete blinding, but the outcome is not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding or incomplete blinding, but the outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

McMillan 1994

Methods	Randomised controlled trial, double-blinded
Participants	38 cancer pts a) 20 pts Mean age 73 yrs b) 18 pts Mean age 70 yrs
Interventions	a) MA 480 mg/d b) Placebo
Outcomes	Weight
Notes	12 weeks of treatment QS = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	" ...the randomisation code was not known to any of the investigators and was only broken at the end of the study"

McMillan 1994 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No data about blinding but unlikely could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No data about blinding but unlikely could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawals were unbalanced but the authors explain all withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported but we did not find this trial in the meta register of clinical trials or http://apps.who.int/trialsearch
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Mwamburi 2004

Methods	Randomised controlled trial
Participants	40 patients with HIV that were receiving HAART (highly active antiretroviral therapy)
Interventions	20 patients MA (800 mg/day) versus 20 patients oxandrolone (20 mg/day) for 2 months
Outcomes	Weight, side effects
Notes	2 patients dropped out at 2 months in the MA group and 4 in the oxandrolone group. Finally 18 patients and 15 patients were used for analysis in the MA and oxandrolone groups, respectively. Cachexia was defined as weight loss > 5% during HAART QS: 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	“Computed generated random numbers”
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias)	Low risk	This study was not blinded but the main outcome is not likely to be influenced by lack of blinding

Mwamburi 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was not blinded but the man outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors describe drop-outs but not the number in each arm
Selective reporting (reporting bias)	Low risk	All outcomes in the paper have been reported
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Oster 1994

Methods	Double-blind, randomised, controlled, multicentre (13)
Participants	100 AIDS pts a) 52 pts = 50 M + 2 F Mean age 40 yrs b) 48 pts = 47 M + 1 F Mean age 40 yrs Mean age 40.00 ± 14 in placebo group and 40 ± 7.2 in MA group
Interventions	a) MA 800 mg/d suspension b) Placebo, suspension
Outcomes	Weight Appetite Triceps skinfold Mid-arm circumference Performance status KI
Notes	12 weeks of treatment QS = 4 Cachexia was defined as loss of 10% or more of ideal body weight

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below

Oster 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients received bottles containing 20-mL portions of a liquid, lemon-lime flavoured suspension of either placebo or 800 mg of megestrol acetate (Megace; Bristol-Myers Squibb, Princeton, New Jersey). Patients were instructed to take the drug orally once daily, 1 hour before or 2 hours after breakfast. Patients and clinicians were blinded to treatment groups throughout the study".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Main outcome was weight and well being
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals were balanced (27 in MA and 22 in placebo group)
Selective reporting (reporting bias)	Low risk	All outcomes were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Sancho-Cuesta 1993

Methods	Randomised controlled trial
Participants	Patients with advanced cancer, anorexia and weight loss
Interventions	50 patients MA 160 mg daily versus 50 patients 320 mg daily for 24 weeks
Outcomes	Weight gain, side effects
Notes	Loss to follow-up not described Cachexia was not defined QS: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	This study was not blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was weight. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding.

Sancho-Cuesta 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described
Selective reporting (reporting bias)	Low risk	All the outcomes described in the study were reported
Other bias	Unclear risk	Report only from old conference proceeding

Schmoll 1991

Methods	Randomised controlled trial, not blinded
Participants	55 patients with advanced cancer Placebo 61 years mean ages MA low-dose 50 years mean ages MA high-dose 58 years mean ages
Interventions	18 patients received high-dose MA (960 mg/daily) versus 20 patients low-dose MA (480 mg/daily) versus 17 patients placebo for 8 weeks
Outcomes	Weight, appetite improvement, adverse events
Notes	Losses to follow-up were 9 in the placebo group, 5 in the low-dose group and 7 in the high-dose group Deaths: 8, 4 and 4 placebo, high-dose and low-dose Not evaluable: 1, 1 and 3 respectively Cachexia was defined as loss of > 5% of ideal body weight QS = 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	This study was not blinded
Blinding of participants and personnel (performance bias)	Low risk	The main outcome was weight. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding

Schmoll 1991 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for missing outcome data are likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	All the pre-specified outcome were published
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Schmoll 1992

Methods	Randomised controlled trial, not blinded
Participants	91 cancer pts a) 29 pts = 18 M + 11 F Mean age 60 yrs (35 to 79) b) 28 pts = 16 M + 12 F Mean age 58 yrs (29 to 78) c) 34 pts = 25 M + 9 F Mean age 60 yrs (41 to 80)
Interventions	a) MA 960 mg/d (high-dose) b) Placebo c) MA 480 mg/d (low-dose)
Outcomes	Weight, appetite improvement, adverse events
Notes	a) Median duration 8 weeks of treatment b) Median duration 6 weeks c) Median duration 7 weeks QS = 2 Withdrawals were deaths, stopped treatment due to size of capsules, and increased appetite after 14 days with lack of motivation to continue the study, but there was no description of which groups they were from Cachexia was defined as loss of > 5% of ideal body weight

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias)	Low risk	This study was not blinded

Schmoll 1992 *(Continued)*

All outcomes		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was weight. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals were high: 44% in the placebo group and 30% in each of the MA groups, but the causes in each group were not described
Selective reporting (reporting bias)	Low risk	All the pre-specified outcomes were published
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Summerbell 1992

Methods	Randomised controlled trial
Participants	14 patients with HIV infection
Interventions	MA 40 mg daily which was increased by 40 mg daily on alternate weeks to a maximum of 160 mg daily if there was no response in weight, or cyproheptadine 12 mg daily for a period of 3 months
Outcomes	Weight, sexual thoughts, arousal and orgasms
Notes	The study was discontinued after 14 patients were enrolled Cachexia was defined as weight loss < 5 kg QS: 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was weight. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding

Summerbell 1992 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was weight. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were studied
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	High risk	The study was discontinued after 14 patients were enrolled, because recruitment was too slow and the majority of patients had diarrhoea or overt infections

Tchekmedyian 1992

Methods	Double-blind, randomised controlled trial
Participants	89 cancer pts a) 49 pts = 28 M + 9 F Mean age 63 yrs b) 40 pts = 18 M + 12 F Mean age 64 yrs
Interventions	a) MA 1600 mg/d, 10 tablets a day, in divided doses b) Placebo 10 tablets
Outcomes	Appetite, categorical scale of 5 levels QoL LAS, 29 items Weight Triceps skinfold Mid-arm circumference
Notes	6 weeks of treatment QS = 4 Cachexia was defined as weight loss of < 5% Patients were considered valuable for analysis if they had at least baseline and 1 follow-up evaluation a month, so 30/40 patients in placebo group and 37/49 patients in MA group. The withdrawals were balanced and included 1 lost to follow-up in the placebo group and 0 in the MA group, cancer progression in 4 and 6 in the placebo and MA group, deep vein thrombosis 0 in the placebo and 2 in the MA group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	6 tables of randomisation were generated
Allocation concealment (selection bias)	Low risk	Central randomisation office
Blinding (performance bias and detection bias)	Low risk	See below

Tchekmedyian 1992 *(Continued)*

All outcomes		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was weight. This is a blinded study and the main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was weight. This is a blinded study and the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawals were balanced across groups
Selective reporting (reporting bias)	Low risk	All the results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Timpone 1997

Methods	Randomised, controlled, multicentre (9)
Participants	50 HIV pts a) 12 pts = 10 M + 2 F Mean age 46 yrs b) 12 pts = 10 M + 2 F Mean age 39 yrs c) 13 pts = 12 M + 1 F Mean age 38 yrs d) 13 pts = 12 M + 1 F Mean age 40 yrs
Interventions	a) MA 750 mg/d, tablets x 1 b) Dronabinol 5 mg/d, tablets x 2 c) MA 750 mg/d, tablets x 1 plus dronabinol 5 mg/d, tablets x 2 d) MA 250 mg/d plus dronabinol 5 mg/d, 2 tablets
Outcomes	Height, weight and vital signs, Karnofsky performance status, complete blood count (CBC), CD4+ T lymphocyte count, chemistry panel, visual analogue scale for hunger (VASH) 3 times per day before meals, visual analogue scale for mood (VASM) at noon, visual analogue scale for nausea (VASN) at noon, and functional assessment for HIV (FAHI) questionnaire
Notes	12 weeks of treatment QS = 3 Losses to follow-up were 6, 2, 5, 7 in Arm 1, Arm 2, Arm 3, and Arm 4 respectively Cachexia was defined as loss of weight of at least 10% or BMI of < 20.5 kg/m^2 for age 18 to 34 years or < 22.5 for age > 35 years (the suggested BMI ranges are 19 to 24, 20 to 25, 21 to 26 and 22 to 27 kg/m^2 for age categories 18 to 24, 25 to 34, 35 to 44 and 45 to 54 years, respectively)

Risk of bias

Bias	Authors' judgement	Support for judgement

Timpone 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Low risk	Patients were sequentially enrolled and the study was performed in an outpatient setting
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This is an open-label study but weight was the main outcome and is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This is an open-label study but weight was the main outcome and is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced
Selective reporting (reporting bias)	Low risk	All the results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Ulutin 2002

Methods	Randomised controlled trial
Participants	119 cancer pts a) 59 pts = 48 M + 11 F Mean age 56 (range 38 to 72) b) 60 pts = 47 M + 13 F Mean age 58 (range 40 to 74)
Interventions	a) MA 160 mg/d orally b) MA 320 mg/d orally in 2 divided doses 12 hrs apart 3 months duration treatment
Outcomes	Weight Appetite (Symptom Distress Scale) QoL (10-point scale) based on patient statements Biochemical levels and side effects
Notes	QS = 2 Cachexia was defined as weight loss > 10% in the last 6 months Only 1 withdrawal was described
Risk of bias	

Ulutin 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was weight. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was weight. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient discontinued treatment due to gastrointestinal intolerance on MA 320 mg
Selective reporting (reporting bias)	Low risk	All the results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Vadell 1998

Methods	Double-blind, randomised, controlled, multicentre (9)
Participants	150 cancer pts a) 49 pts = 38 M + 11 F Mean age 66 yrs b) 51 pts = 42 M + 9 F Mean age 63 yrs c) 50 pts = 31 M + 19 F Mean age 65 yrs
Interventions	a) MA 480 mg/d, 3 tablets b) Placebo, 3 tablets c) MA 160 mg/d, 1 tablet + placebo 2 tablets
Outcomes	Weight Mid-arm circumference Triceps skinfold QoL Performance status Karnofsky Index
Notes	12 weeks of treatment QS = 4

Vadell 1998 *(Continued)*

	Follow-up 12 weeks; 64 patients remain at 12 weeks. Losses were homogeneously distributed among the 3 groups (16 in the placebo group, 13 in MA 160 mg and 14 in 480 mg/daily) Cachexia was defined as weight loss < 5%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants received 3 tablets to assure the blinding and the main outcome was weight
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was weight
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 64 patients remained at 12 weeks but the losses were described as balanced in all groups
Selective reporting (reporting bias)	Low risk	All the outcomes were described
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Von Roenn 1994

Methods	Double-blind, randomised, controlled, multicentre
Participants	271 patients with AIDS who had substantial weight loss and anorexia 270 M and 1 F a) 75 pts = 75 M Mean age 38 yrs b) 75 pts = 75 M Mean age 39 yrs c) 82 pts = 81 M + 1 F Mean age 39 yrs d) 38 pts = 38 M Mean age 38 yrs
Interventions	a) MA 800 mg/d, suspension b) MA 400 mg/d, suspension c) MA 100 mg/ d, suspension

Von Roenn 1994 *(Continued)*

	d) Placebo, suspension
Outcomes	Weight Appetite Mid-arm circumference Triceps skinfold QoL by linear analogue self assessment questionnaire
Notes	12 weeks of treatment QS = 2 Clinically significant weight loss was defined as a decrease of 20% from usual body weight, or as 10% below ideal body weight for patients whose premorbid weight was greater than ideal body weight, or as a loss of 10% or more of usual body weight for those whose premorbid weight was below ideal body weight. Patients with stable weight or excessive weight gain could be removed from the study after completing the 12-week trial period. Patients otherwise continued on their assigned treatment as long as they did not have additional weight loss of more than 10% of their baseline body weight. 75 were not evaluable for the efficacy analysis (27 patients did not meet the premorbid weight loss requirement, 46 patients had no follow-up visits and 7 patients had only 1 follow-up visit. Authors do not describe how many patients were in each arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was weight. This is a blinded study and the main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was weight. This is a blinded study and the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No data on balance of withdrawals in each arm
Selective reporting (reporting bias)	Low risk	All the results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Wanke 2007

Methods	Randomised controlled trial, open-label
Participants	63 HIV-infected adults with weight loss in South Africa, India and the United States
Interventions	MA concentrated suspension (575 mg/5 ml; MA-CS) was compared with traditional MA oral suspension (800 mg/20 ml; MA-OS) 12-week trial
Outcomes	Body weight, quality of life including appetite, safety
Notes	Cachexia was defined as "body weight of less than 90% of the ideal body weight from the Metropolitan Height and Weight Table (1999 version)" QS: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Low risk	Central allocation. This was a multicentre study.
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Weight was the main outcome. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Weight was the main outcome. This is not a blinded study but the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants in 575 mg MA group withdrew because of an adverse event and 3 participants in the MA 800 mg because an adverse event
Selective reporting (reporting bias)	Low risk	All the results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Weisberg 2002

Methods	Double-blind, randomised, controlled, multicentre (18)
Participants	145 COPD pts a) 72 pts = 46 M + 26 F Mean age 68 yrs b) 73 pts = 45 M + 28 F

Weisberg 2002 *(Continued)*

	Mean age 66 yrs
Interventions	a) MA 800 mg/d, suspension b) Placebo, suspension
Outcomes	Weight Triceps skinfold Mid-arm circumference Appetite
Notes	8 weeks of treatment QS = 3 Cachexia was defined as "Underweight COPD patients (< 95% of ideal body weight) > 40 years of age in a stable phase of their disease were recruited at 18 study centres"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was a functional test (spirometry)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was a functional test (spirometry)
Incomplete outcome data (attrition bias) All outcomes	Low risk	17 withdrawals but balanced in 2 arms
Selective reporting (reporting bias)	Low risk	All the results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

Yeh 2000

Methods	Double-blind randomised controlled trial
Participants	69 patients with geriatric cachexia a) 36 pts = 35 M + 1 F Mean age 76 yrs b) 33 pts = 31 M + 2 F

Yeh 2000 *(Continued)*

	Mean age 76 yrs
Interventions	a) MA 800 mg/d, suspension b) Placebo, suspension 12 weeks
Outcomes	Weight Appetite Sense of well being (SOWB), enjoyment of life, laboratory nutrition parameter and adverse events were measured
Notes	Follow_up 13 weeks QS = 3 Cachexia was defined as experienced weight loss > 5% of their usual body weight during the previous 3 months, or had a body weight of 20% below their ideal body weight (based on the tables of the Metropolitan Life Insurance Company and the Gerontology Research Center)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding (performance bias and detection bias) All outcomes	Low risk	See below
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The main outcome was weight. This is a blinded study and the main outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main outcome was weight. This is a blinded study and the main outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawals were balanced
Selective reporting (reporting bias)	Low risk	All the results were available
Other bias	Unclear risk	Insufficient information to permit judgement of low risk or high risk

BMI: body mass index
COPD: chronic obstructive pulmonary disease
d: day
DRO: dronabinol
EPA: eicosapentaenoic acid
F: female
FAACT: functional assessment of anorexia/cachexia therapy

HAART: highly active antiretroviral therapy
KI: Karnofsky Index
LASA: linear analogue self assessment
M: male
MA: megestrol acetate
NCCTG: The North Central Cancer Treatment Group
pts: patientsPS: Performance Status
QoL: quality of life
QS: quality score (Oxford Quality Scale)
SD: standard deviation
SSA: subjective sense of appetiteTIQ: Therapy Impact Questionnaire
VAS: visual analogue scale
yrs: years

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aguilera 2001	This study is a review
Aisner 1988	This study is a review
Anonymous 1995	This study is a review
Ansfield 1982	Prospective study
Argiles 2007	This study is a review
Argiles 2008	This study is a review
Argiles 2010	This study is a review
Behl 2007	This study is a review
Bossola 2006	This study is a review
Bossola 2009	This study is a review
Bruera 1990	This is a cross-over study
Bruera 1992a	This study is a review
Bruera 1998	This is a cross-over study
Bruera 1998a	This study is a review
Cardona 2006	This study is a review
Carroll 2007	This study is a systematic review
Cat 1994	This study is a review
Celik 2009	This study is a review
Chen 1997	This is a RCT of patients with head and neck cancers but only 18% of them were underweight; moreover 11% were overweight

Study	Reason for exclusion
Chlebowski 1996	This study is a review
Costero 2004	This is just a cohort study without any comparison group
Cruz 1990	Patients not described as 'patients with cachexia'
Cuerda 1998	This study is a review
Desport 2000	This study is a clinical guideline
Elovic 2000	This study is a review
Erkurt 2000	This study included a small proportion of patients without weight loss in the previous 6 months. In addition, these patients were not balanced in both groups. 33 patients received oral nutrition support: 27% in the MA and 72% in the placebo group
Farmer 2005	Patients not described as 'patients with cachexia'
Farrar 1999	This study is a review
Fearon 2002	This study is a review
Fossati 1998	This study is a systematic review of treatment for metastatic breast cancer
Fox 2009	This study is a review
Freyer 1996	This study is a review
Freyer 1996a	This study is a review
Gaducci 2001	This study is a review
Garg 2010	This study is a systematic review
Gullett	This study is a review
Hanson 2011	This study is a systematic review
Haren 2006	This study is a review
Hellerstein 1990	This study is a review
Hoffman 1998	This is not a trial: cohort study
Inui 2002	This study is a review
Jatoi 2001	This study is a review
Kalantar-Zadeh 2008	This study is a review
Karcic 2002	This study is a review
Khojasteh 1996	This is a small clinical trial that compared combined nortriptyline (25 to 50 mg Q HS PO) + MA (400 mg BID PO) versus MA (400 mg BID PO)

Study	Reason for exclusion
Krznaric 2007	This is a clinical guideline
Kumar 2010	This study is a review
Lai 1994	Patients did not have cachexia or any weight loss
Lelli 2003	This study is a review
Lesniak 2008	This study is a systematic review
Loprinzi 1992	This study is a review
Loprinzi 1992a	This study is a review
Loprinzi 1993	This study Is not a trial, is a cohort study without any control group
Loprinzi 1995	This study is a review
Mak 2007	This study is a review
Malone 2005	This study is a review
Maltoni 2001a	This study is a systematic review
Mantovani 1998a	This study is a review
Mantovani 2001	This study is a review
Mantovani 2008	This is a RCT with 5 arms; in one of them patients received medroxyprogesterone acetate or megestrol acetate
Mantovani 2010	This is a clinical abstract in proceedings
Marchand 2000	This is a RCT cross-over study
Mateen 2006	This study is a review
McHugh 2011	This study is a review
McMillan 1999	This is a trial that compared MA plus placebo versus MA plus ibuprofen in patients with gastrointestinal cancer with weight loss
McQuellon 2002	Patients not described as 'patients with cachexia'
Monfared 2009	Patients not described as 'patients with cachexia' and the outcome was levels of albumin
Morley 2002	This study is a review
Morán 1998	This is a trial with malnourished post necrotic (VHC) patients, but cachexia was not described. This is an abstract without any data on the placebo group for appetite.
Mulligan 2007	This study compared patients allocated to receive megestrol acetate plus testosterone versus placebo

Study	Reason for exclusion
Muss 1990	Patients were not described as having cachexia-anorexia related to cancer. This is a trial in breast cancer.
Navari 2010	This is a RCT that compared MA plus olanzapine versus MA
Nelson 2002	This is not a trial: cohort study without comparison group
Osoba 1994	All patients received MA, without a control group
Pardo 2003a	Patients were not described as 'patients with cachexia'
Pardo 2006	Patients were not described as 'patients with cachexia'
Pascual 2004	This study is a systematic review
Pruthi 2007	This study is a clinical guideline
Reuben 2005	Patients were older persons (mean age 83) discharged from an acute hospital with fair or poor appetite
Ross 2001	This study is a review
Rowland 1996	This is a trial that compared chemotherapy in cancer patients in both groups with MA versus placebo in patients who started chemotherapy for small cell lung cancer. Patients were not described as 'patients with cachexia/anorexia'. Moreover most of them (85%) had weight loss < 10%. This study was included in the previous review.
Ruiz-Garcia 2002	This study is a systematic review about megestrol and weight gain in cancer patients
Sanz-Ortiz 2004	This study is a review
Schacter 1989	This study is a review
Schmoll 1992a	This study is a review
Simmons 2004	Patients not described as 'patients with cachexia'
Skarlos 1993	This is a cohort study
Spaulding 1989	This study is a review
Sullivan 2007	Patients were older than 65 with functional decline without any criteria for cachexia
Tchekmedyian 1986	This is not a trial and patients were women with advanced breast cancer
Tchekmedyian 1990	This is not a trial
Tchekmedyian 1991	This study is a review
Tchekmedyian 1993	This study is a review
Tchekmedyian 1993a	This study is a review
Tchekmedyian 2006	This study is a review

Study	Reason for exclusion
Thomas 2006	This study is a clinical guideline
Tisdale 1993	This study is a review
Tisdale 2006	This study is a review
Tomiska 2003	This is a RCT that compared 2 doses of MA in cancer anorexia/cachexia syndrome, but results were described as improvement of appetite, gain of weight etc. in all evaluated patients
Vigano 1994	This study is a review
von Haehling 2009	This study is a review of cardiac cachexia
Von Roenn 1994a	This study is a review
Vyzula 1997	This study is a review
Westman 1999	This is a trial in malnourished cancer patients but 1/3 of patients in the MA and placebo group had not developed cachexia
Yavuzsen 2005	This study is a systematic review
Yeh 2004	This study involved the same participants as Yeh 2000, in which they measured different outcomes
Yeh 2006	This study is a review
Yeh 2007	This study is a review
Yeh 2010	Patients not described as 'patients with cachexia'
Zeca 1995	This is a trial that included patients with cancer and anorexia. Cachexia was not needed. This is a small trial, published in proceedings, with two phases. In first phase patients received 320 mg/d of MA. In the second phase all patients received different dosages of MA according to the response to treatment.

BID: twice a day
d: day
MA: megestrol acetate
PO: orally
RCT: randomised controlled trial

DATA AND ANALYSES

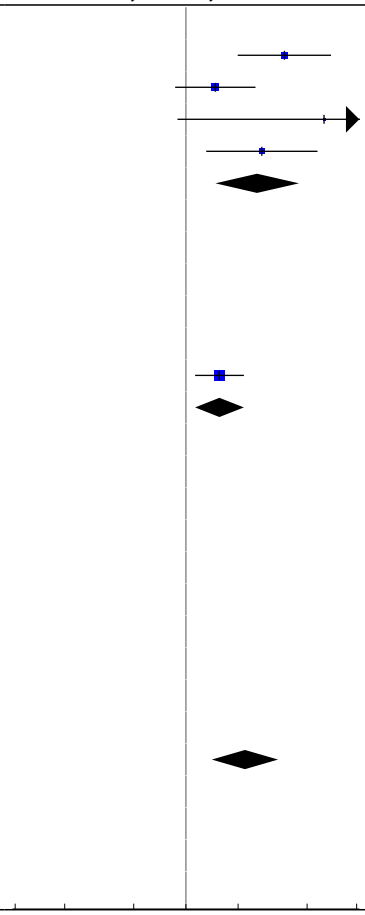
Comparison 1. Megestrol acetate versus placebo (ITT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Appetite improvement	5	699	Risk Ratio (M-H, Random, 95% CI)	2.19 [1.41, 3.40]
1.1 Cancer	4	429	Risk Ratio (M-H, Random, 95% CI)	2.57 [1.48, 4.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 AIDS	1	270	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.13, 2.16]
1.3 Other underlying pathology	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Appetite gain	2	75	Std. Mean Difference (IV, Random, 95% CI)	0.91 [0.43, 1.39]
2.1 Cancer	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 AIDS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Other underlying pathology	2	75	Std. Mean Difference (IV, Random, 95% CI)	0.91 [0.43, 1.39]
3 Weight improvement	10	1106	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.08, 2.11]
3.1 Cancer	8	767	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.06, 2.26]
3.2 AIDS	1	270	Risk Ratio (M-H, Random, 95% CI)	2.15 [1.14, 4.04]
3.3 Other underlying pathology	1	69	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.30, 1.70]
4 Weight gain	8	552	Mean Difference (IV, Random, 95% CI)	1.93 [0.95, 2.91]
4.1 Cancer	3	227	Mean Difference (IV, Random, 95% CI)	1.63 [0.87, 2.38]
4.2 AIDS	1	81	Mean Difference (IV, Random, 95% CI)	4.26 [2.70, 5.82]
4.3 Other underlying pathology	4	244	Mean Difference (IV, Random, 95% CI)	1.47 [0.06, 2.87]
5 Quality of life improvement	4	670	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.09, 2.92]
5.1 Cancer	2	300	Risk Ratio (M-H, Random, 95% CI)	1.91 [1.02, 3.59]
5.2 AIDS	2	370	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.47, 4.69]
5.3 Other underlying pathology	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Quality of life gain	2	70	Std. Mean Difference (IV, Random, 95% CI)	0.50 [-0.13, 1.13]
6.1 Cancer	1	33	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.51, 0.86]
6.2 AIDS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Other underlying pathology	1	37	Std. Mean Difference (IV, Random, 95% CI)	0.82 [0.14, 1.50]

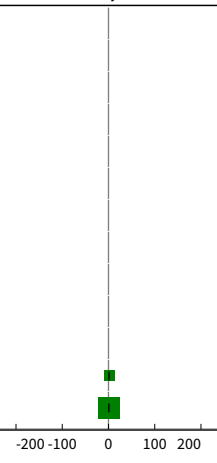
Analysis 1.1. Comparison 1 Megestrol acetate versus placebo (ITT), Outcome 1 Appetite improvement.

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Cancer					
Feliu 1992	38/76	10/74		21.61%	3.7[1.99,6.87]
Loprinzi 1990b	24/67	16/66		24.28%	1.48[0.87,2.52]
Schmoll 1991	14/38	1/17		4.48%	6.26[0.89,43.87]
Schmoll 1992	37/63	6/28		18.27%	2.74[1.31,5.74]
Subtotal (95% CI)	**244**	**185**		**68.64%**	**2.57[1.48,4.49]**
Total events: 113 (Megestrol acetate), 33 (Placebo)					
Heterogeneity: Tau^2=0.16; Chi^2=6.32, df=3(P=0.1); I^2=52.54%					
Test for overall effect: Z=3.33(P=0)					
1.1.2 AIDS					
Von Roenn 1994	181/232	19/38		31.36%	1.56[1.13,2.16]
Subtotal (95% CI)	**232**	**38**		**31.36%**	**1.56[1.13,2.16]**
Total events: 181 (Megestrol acetate), 19 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.68(P=0.01)					
1.1.3 Other underlying pathology					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol acetate), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**476**	**223**		**100%**	**2.19[1.41,3.4]**
Total events: 294 (Megestrol acetate), 52 (Placebo)					
Heterogeneity: Tau^2=0.13; Chi^2=9.77, df=4(P=0.04); I^2=59.05%					
Test for overall effect: Z=3.5(P=0)					
Test for subgroup differences: Chi^2=2.32, df=1 (P=0.13), I^2=56.86%					

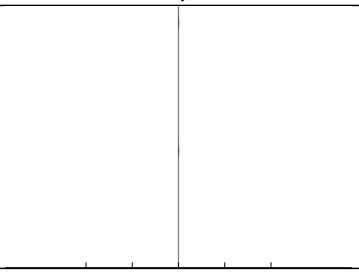


Analysis 1.2. Comparison 1 Megestrol acetate versus placebo (ITT), Outcome 2 Appetite gain.

Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.2.1 Cancer							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.2.2 AIDS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.2.3 Other underlying pathology							
Herrejon 2011	13	3.5 (1.9)	14	0.9 (2.4)		34.03%	1.12[0.3,1.94]
Yeh 2000	24	1.2 (1)	24	0.3 (1.2)		65.97%	0.8[0.21,1.39]

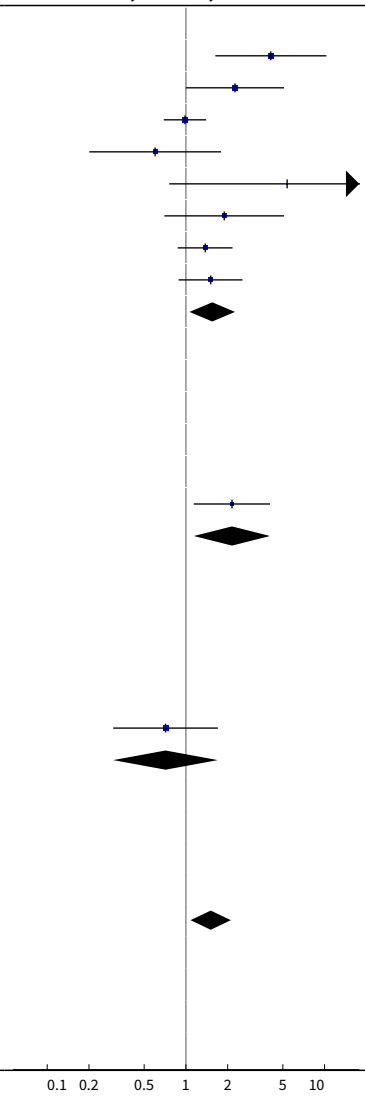


Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Subtotal ***	**37**		**38**			**100%**	**0.91[0.43,1.39]**
Heterogeneity: Tau²=0; Chi²=0.39, df=1(P=0.53); I²=0%							
Test for overall effect: Z=3.71(P=0)							
Total ***	**37**		**38**			**100%**	**0.91[0.43,1.39]**
Heterogeneity: Tau²=0; Chi²=0.39, df=1(P=0.53); I²=0%							
Test for overall effect: Z=3.71(P=0)							
Test for subgroup differences: Not applicable							



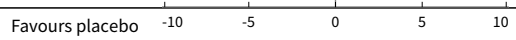
Analysis 1.3. Comparison 1 Megestrol acetate versus placebo (ITT), Outcome 3 Weight improvement.

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Cancer					
Feliu 1992	21/76	5/74		8.07%	4.09[1.63,10.27]
Fietkau 1996	14/31	6/30		9.33%	2.26[1,5.1]
Loprinzi 1990b	32/67	32/66		16.92%	0.99[0.69,1.4]
McMillan 1994	4/20	6/18		6.46%	0.6[0.2,1.79]
Schmoll 1991	12/38	1/17		2.56%	5.37[0.76,38.04]
Schmoll 1992	17/63	4/28		7.34%	1.89[0.7,5.1]
Tchekmedyian 1992	27/49	16/40		15.03%	1.38[0.87,2.17]
Vadell 1998	38/99	13/51		13.66%	1.51[0.89,2.56]
Subtotal (95% CI)	**443**	**324**		**79.37%**	**1.55[1.06,2.26]**
Total events: 165 (Megestrol acetate), 83 (Placebo)					
Heterogeneity: Tau²=0.14; Chi²=15.76, df=7(P=0.03); I²=55.58%					
Test for overall effect: Z=2.29(P=0.02)					
1.3.2 AIDS					
Von Roenn 1994	105/232	8/38		11.96%	2.15[1.14,4.04]
Subtotal (95% CI)	**232**	**38**		**11.96%**	**2.15[1.14,4.04]**
Total events: 105 (Megestrol acetate), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.37(P=0.02)					
1.3.3 Other underlying pathology					
Yeh 2000	7/36	9/33		8.68%	0.71[0.3,1.7]
Subtotal (95% CI)	**36**	**33**		**8.68%**	**0.71[0.3,1.7]**
Total events: 7 (Megestrol acetate), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.44)					
Total (95% CI)	**711**	**395**		**100%**	**1.51[1.08,2.11]**
Total events: 277 (Megestrol acetate), 100 (Placebo)					
Heterogeneity: Tau²=0.14; Chi²=19.98, df=9(P=0.02); I²=54.95%					
Test for overall effect: Z=2.4(P=0.02)					
Test for subgroup differences: Chi²=4.09, df=1 (P=0.13), I²=51.14%					



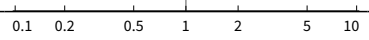
Analysis 1.4. Comparison 1 Megestrol acetate versus placebo (ITT), Outcome 4 Weight gain.

Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.4.1 Cancer							
De Conno 1998	17	1.1 (2)	16	-0.3 (1)		15.33%	1.4[0.35,2.45]
Fietkau 1996	31	-0.9 (3.6)	30	-3.2 (3.2)		11.89%	2.3[0.59,4.01]
Loprinzi 1990b	67	1.4 (5)	66	-0.2 (3)		13.49%	1.58[0.18,2.98]
Subtotal ***	**115**		**112**			**40.71%**	**1.63[0.87,2.38]**
Heterogeneity: Tau²=0; Chi²=0.78, df=2(P=0.68); I²=0%							
Test for overall effect: Z=4.23(P<0.0001)							
1.4.2 AIDS							
Von Roenn 1994	53	3.5 (4.3)	28	-0.7 (2.9)		12.62%	4.26[2.7,5.82]
Subtotal ***	**53**		**28**			**12.62%**	**4.26[2.7,5.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.34(P<0.0001)							
1.4.3 Other underlying pathology							
Eubanks 2002	10	5.3 (3.6)	7	1.5 (1.6)		8.32%	3.8[1.27,6.33]
Herrejon 2011	15	2.3 (3.4)	16	0.1 (1.2)		11.43%	2.2[0.4,4]
Weisberg 2002	72	1.2 (1.4)	73	0.6 (1.1)		18.02%	0.6[0.19,1.01]
Yeh 2000	25	1.1 (5)	26	0.9 (3.5)		8.91%	0.14[-2.23,2.51]
Subtotal ***	**122**		**122**			**46.67%**	**1.47[0.06,2.87]**
Heterogeneity: Tau²=1.27; Chi²=8.85, df=3(P=0.03); I²=66.12%							
Test for overall effect: Z=2.04(P=0.04)							
Total ***	**290**		**262**			**100%**	**1.93[0.95,2.91]**
Heterogeneity: Tau²=1.34; Chi²=30.48, df=7(P<0.0001); I²=77.03%							
Test for overall effect: Z=3.85(P=0)							
Test for subgroup differences: Chi²=9.51, df=1 (P=0.01), I²=78.96%							

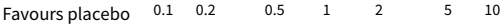


Analysis 1.5. Comparison 1 Megestrol acetate versus placebo (ITT), Outcome 5 Quality of life improvement.

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Cancer					
Feliu 1992	26/76	10/74		32.26%	2.53[1.31,4.88]
Vadell 1998	18/99	7/51		25%	1.32[0.59,2.96]
Subtotal (95% CI)	**175**	**125**		**57.26%**	**1.91[1.02,3.59]**
Total events: 44 (Megestrol acetate), 17 (Placebo)					
Heterogeneity: Tau²=0.07; Chi²=1.5, df=1(P=0.22); I²=33.13%					
Test for overall effect: Z=2.02(P=0.04)					
1.5.2 AIDS					
Oster 1994	5/52	6/48		15.39%	0.77[0.25,2.36]
Von Roenn 1994	91/232	6/38		27.35%	2.48[1.17,5.27]
Subtotal (95% CI)	**284**	**86**		**42.74%**	**1.49[0.47,4.69]**

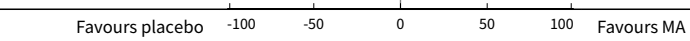


Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 96 (Megestrol acetate), 12 (Placebo)					
Heterogeneity: Tau²=0.46; Chi²=2.94, df=1(P=0.09); I²=65.99%					
Test for overall effect: Z=0.68(P=0.49)					
1.5.3 Other underlying pathology					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol acetate), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**459**	**211**		**100%**	**1.78[1.09,2.92]**
Total events: 140 (Megestrol acetate), 29 (Placebo)					
Heterogeneity: Tau²=0.08; Chi²=4.5, df=3(P=0.21); I²=33.35%					
Test for overall effect: Z=2.3(P=0.02)					
Test for subgroup differences: Chi²=0.14, df=1 (P=0.71), I²=0%					



Analysis 1.6. Comparison 1 Megestrol acetate versus placebo (ITT), Outcome 6 Quality of life gain.

Study or subgroup	Megestrol acetate N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.6.1 Cancer							
De Conno 1998	17	-0.6 (8.3)	16	-1.9 (5.4)		49.65%	0.18[-0.51,0.86]
Subtotal ***	**17**		**16**			**49.65%**	**0.18[-0.51,0.86]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.51(P=0.61)							
1.6.2 AIDS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.6.3 Other underlying pathology							
Yeh 2000	17	7.8 (4.2)	20	4.7 (3.3)		50.35%	0.82[0.14,1.5]
Subtotal ***	**17**		**20**			**50.35%**	**0.82[0.14,1.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.38(P=0.02)							
Total ***	**34**		**36**			**100%**	**0.5[-0.13,1.13]**
Heterogeneity: Tau²=0.09; Chi²=1.71, df=1(P=0.19); I²=41.51%							
Test for overall effect: Z=1.56(P=0.12)							
Test for subgroup differences: Chi²=1.71, df=1 (P=0.19), I²=41.51%							

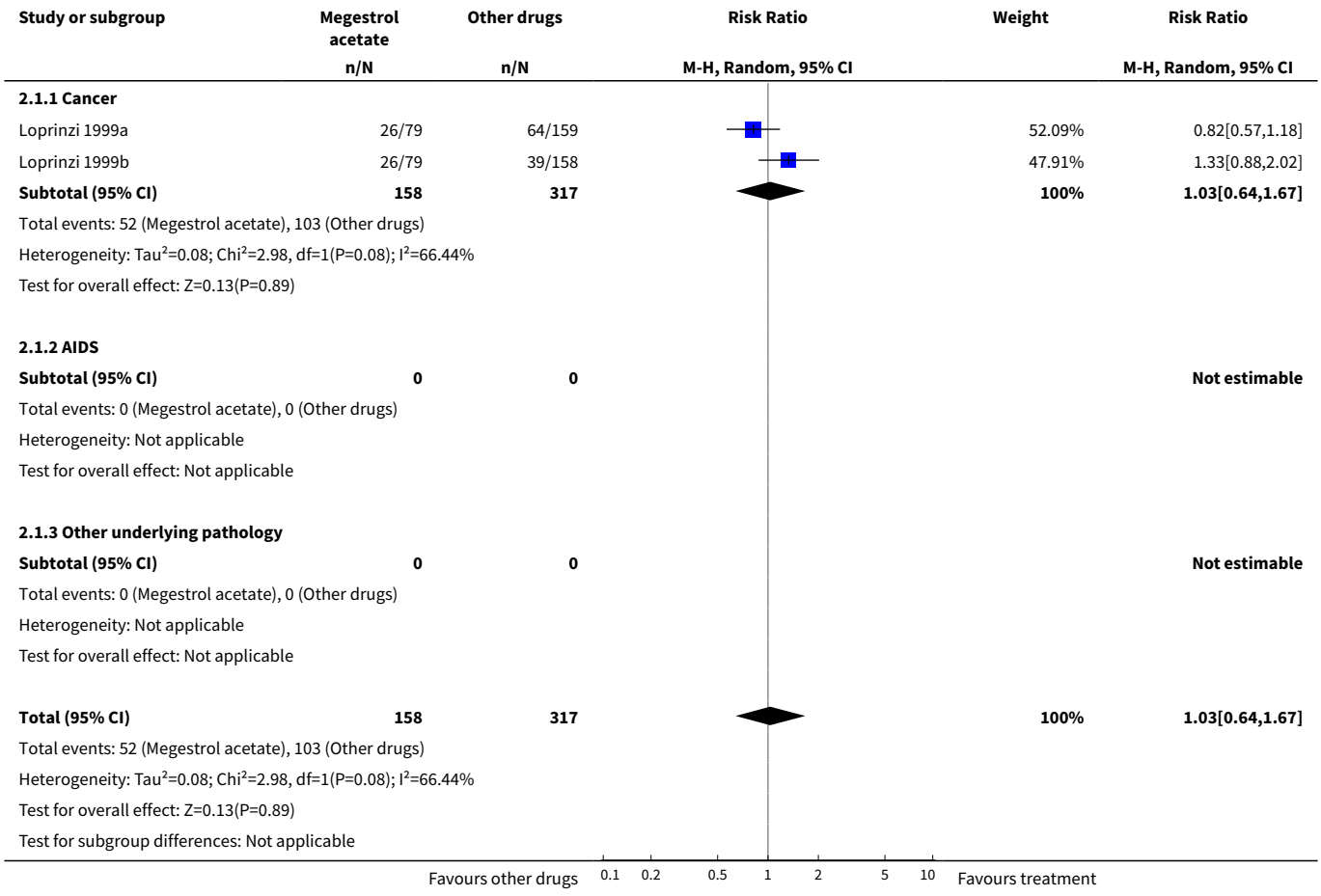


Comparison 2. Megestrol acetate versus other drugs (ITT)

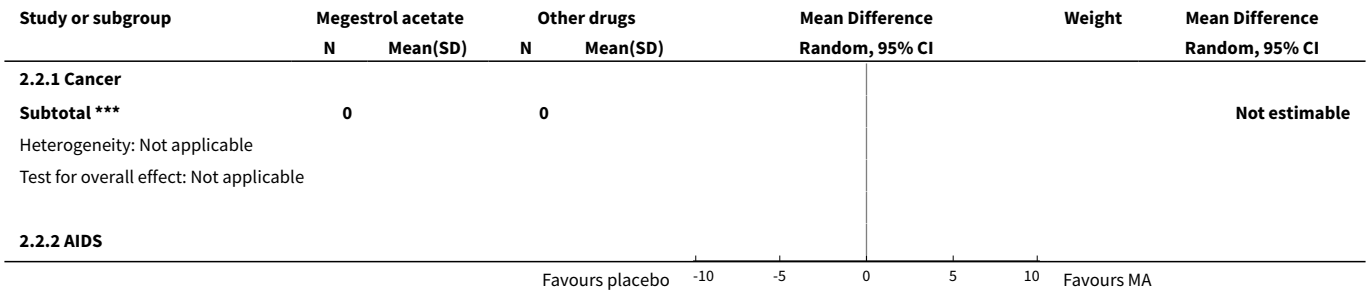
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Appetite improvement	2	475	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.67]
1.1 Cancer	2	475	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.67]
1.2 AIDS	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Other underlying pathology	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Appetite gain	1	9	Mean Difference (IV, Random, 95% CI)	1.60 [-1.28, 4.48]
2.1 Cancer	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 AIDS	1	9	Mean Difference (IV, Random, 95% CI)	1.60 [-1.28, 4.48]
2.3 Other underlying pathology	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Weight improvement	7	1131	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.09, 2.52]
3.1 Cancer	4	1067	Risk Ratio (M-H, Random, 95% CI)	2.49 [1.54, 4.00]
3.2 AIDS	3	64	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.84, 1.61]
3.3 Other underlying pathology	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Weight gain	5	541	Mean Difference (IV, Random, 95% CI)	2.50 [0.37, 4.64]
4.1 Cancer	2	475	Mean Difference (IV, Random, 95% CI)	0.61 [-0.15, 1.38]
4.2 AIDS	3	66	Mean Difference (IV, Random, 95% CI)	4.85 [-0.79, 10.49]
4.3 Other underlying pathology	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Quality of life improvement	2	475	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.77, 1.44]
5.1 Cancer	2	475	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.77, 1.44]
5.2 AIDS	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Other underlying pathology	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Quality of life gain	1	311	Std. Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.02, 0.43]
6.1 Cancer	1	311	Std. Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.02, 0.43]
6.2 AIDS	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Other underlying pathology	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

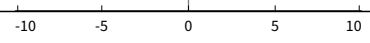
Analysis 2.1. Comparison 2 Megestrol acetate versus other drugs (ITT), Outcome 1 Appetite improvement.



Analysis 2.2. Comparison 2 Megestrol acetate versus other drugs (ITT), Outcome 2 Appetite gain.

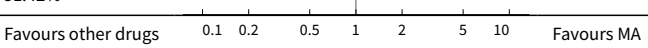


Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Other drugs N	Other drugs Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Batterham 2001	4	3.3 (2.8)	5	1.7 (1)		100%	1.6[-1.28,4.48]
Subtotal ***	**4**		**5**			**100%**	**1.6[-1.28,4.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.09(P=0.28)							
2.2.3 Other underlying pathology							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**4**		**5**			**100%**	**1.6[-1.28,4.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.09(P=0.28)							
Test for subgroup differences: Not applicable							

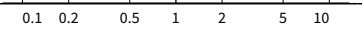


Analysis 2.3. Comparison 2 Megestrol acetate versus other drugs (ITT), Outcome 3 Weight improvement.

Study or subgroup	Megestrol acetate n/N	Other drugs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Cancer					
Jatoi 2002	16/159	5/152		11.34%	3.06[1.15,8.14]
Jatoi 2004	25/140	8/141		15.06%	3.15[1.47,6.74]
Loprinzi 1999a	6/79	8/159		10.73%	1.51[0.54,4.2]
Loprinzi 1999b	5/79	5/158		8.54%	2[0.6,6.71]
Subtotal (95% CI)	**457**	**610**		**45.67%**	**2.49[1.54,4]**
Total events: 52 (Megestrol acetate), 26 (Other drugs)					
Heterogeneity: Tau^2=0; Chi^2=1.59, df=3(P=0.66); I^2=0%					
Test for overall effect: Z=3.75(P=0)					
2.3.2 AIDS					
Batterham 2001	4/4	5/6		21.42%	1.15[0.71,1.86]
Mwamburi 2004	13/20	12/20		21.51%	1.08[0.67,1.75]
Summerbell 1992	5/7	3/7		11.4%	1.67[0.63,4.42]
Subtotal (95% CI)	**31**	**33**		**54.33%**	**1.16[0.84,1.61]**
Total events: 22 (Megestrol acetate), 20 (Other drugs)					
Heterogeneity: Tau^2=0; Chi^2=0.62, df=2(P=0.73); I^2=0%					
Test for overall effect: Z=0.92(P=0.36)					
2.3.3 Other underlying pathology					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol acetate), 0 (Other drugs)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**488**	**643**		**100%**	**1.66[1.09,2.52]**
Total events: 74 (Megestrol acetate), 46 (Other drugs)					
Heterogeneity: Tau^2=0.15; Chi^2=12.35, df=6(P=0.05); I^2=51.42%					



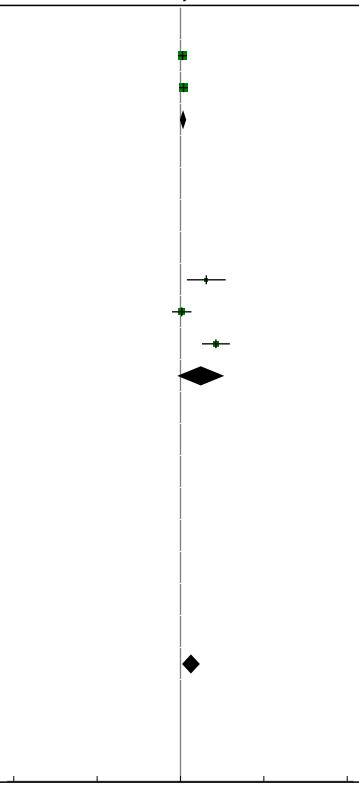
Study or subgroup	Megestrol acetate	Other drugs	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=2.38(P=0.02)					
Test for subgroup differences: Chi²=6.68, df=1 (P=0.01), I²=85.04%					



Favours other drugs — Favours MA

Analysis 2.4. Comparison 2 Megestrol acetate versus other drugs (ITT), Outcome 4 Weight gain.

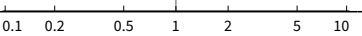
Study or subgroup	Megestrol acetate		Other drugs		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.4.1 Cancer							
Loprinzi 1999a	79	2.5 (4.5)	159	2 (3.2)		25.46%	0.49[-0.61,1.59]
Loprinzi 1999b	79	2.5 (4.5)	158	1.8 (2.6)		25.59%	0.73[-0.33,1.79]
Subtotal ***	**158**		**317**			**51.06%**	**0.61[-0.15,1.38]**
Heterogeneity: Tau²=0; Chi²=0.09, df=1(P=0.76); I²=0%							
Test for overall effect: Z=1.58(P=0.12)							
2.4.2 AIDS							
Batterham 2001	4	10.2 (4.5)	5	4 (1.7)		11.9%	6.19[1.53,10.85]
Mwamburi 2004	18	2.8 (4.3)	15	2.5 (2.4)		20.63%	0.3[-2.03,2.63]
Timpone 1997	12	6.5 (3.8)	12	-2 (4.5)		16.41%	8.5[5.16,11.84]
Subtotal ***	**34**		**32**			**48.94%**	**4.85[-0.79,10.49]**
Heterogeneity: Tau²=21.64; Chi²=17.16, df=2(P=0); I²=88.35%							
Test for overall effect: Z=1.69(P=0.09)							
2.4.3 Other underlying pathology							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**192**		**349**			**100%**	**2.5[0.37,4.64]**
Heterogeneity: Tau²=4.36; Chi²=25.57, df=4(P<0.0001); I²=84.36%							
Test for overall effect: Z=2.3(P=0.02)							
Test for subgroup differences: Chi²=2.13, df=1 (P=0.14), I²=53.07%							



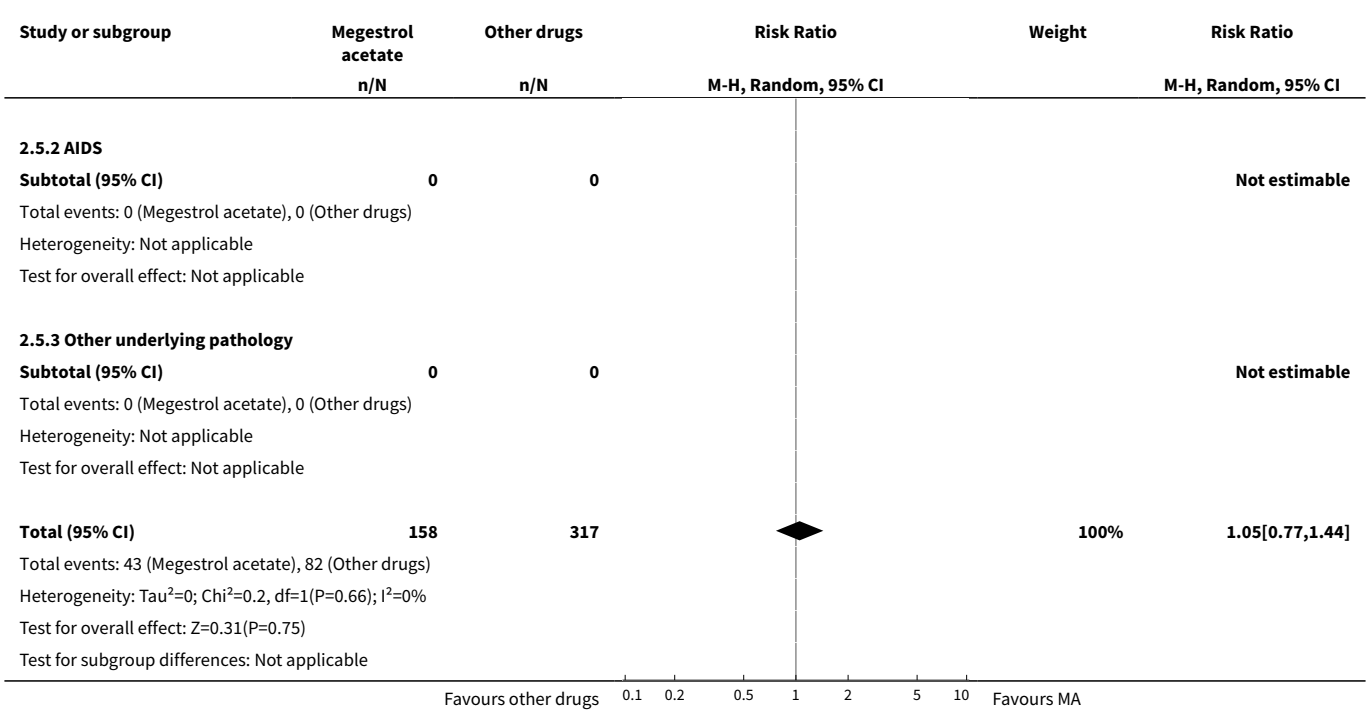
Favours other drugs — Favours MA

Analysis 2.5. Comparison 2 Megestrol acetate versus other drugs (ITT), Outcome 5 Quality of life improvement.

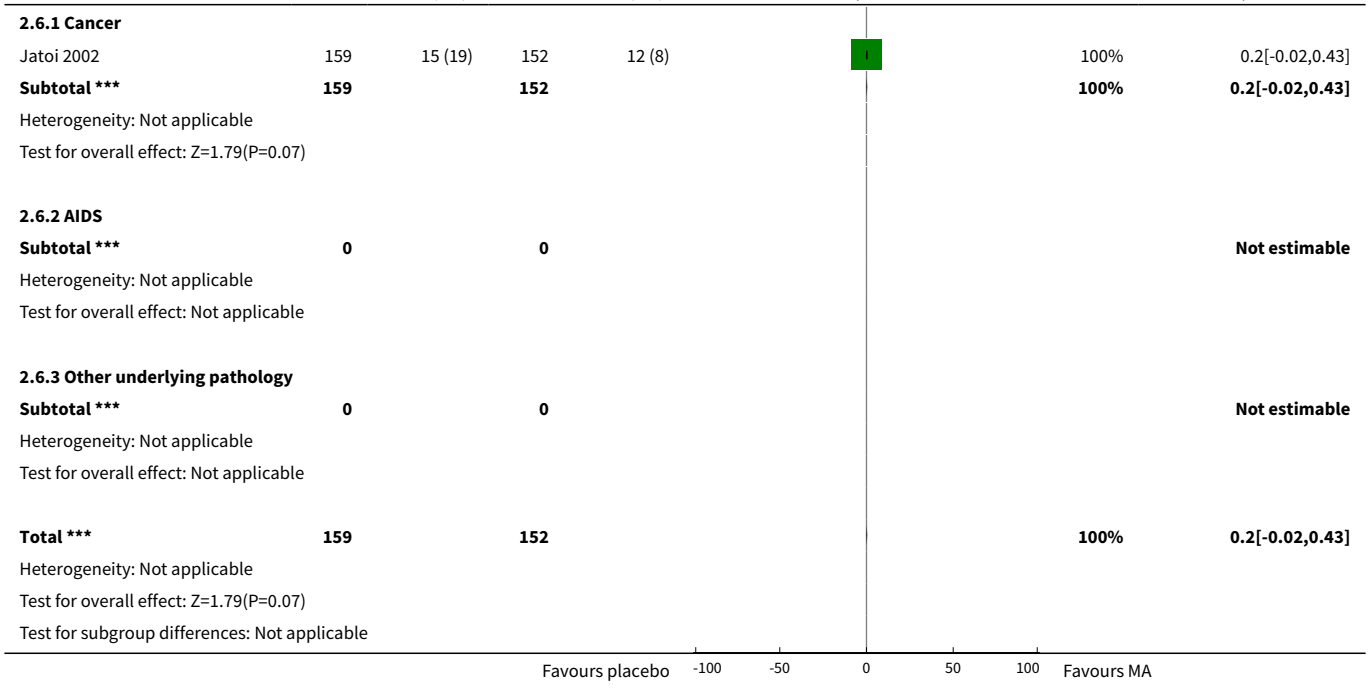
Study or subgroup	Megestrol acetate	Other drugs	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
2.5.1 Cancer					
Loprinzi 1999a	22/79	45/159		53.32%	0.98[0.64,1.52]
Loprinzi 1999b	21/79	37/158		46.68%	1.14[0.71,1.8]
Subtotal (95% CI)	**158**	**317**		**100%**	**1.05[0.77,1.44]**
Total events: 43 (Megestrol acetate), 82 (Other drugs)					
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.66); I²=0%					
Test for overall effect: Z=0.31(P=0.75)					



Favours other drugs — Favours MA



Analysis 2.6. Comparison 2 Megestrol acetate versus other drugs (ITT), Outcome 6 Quality of life gain.

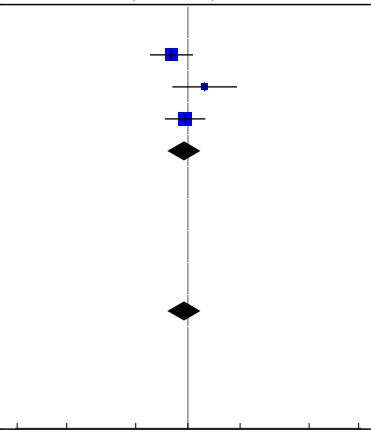


Comparison 3. Megestrol acetate versus megestrol acetate (ITT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Appetite improvement	3	304	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.18]
1.1 Cancer	3	304	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.18]
2 Weight improvement	6	812	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.93]
2.1 Cancer	6	812	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.93]
3 Weight improvement 160 mg versus other higher doses	4	407	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 0.99]
3.1 Cancer	4	407	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 0.99]
4 Weight gain	2	283	Mean Difference (IV, Random, 95% CI)	-0.94 [-3.33, 1.45]
4.1 Cancer	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 AIDS	2	283	Mean Difference (IV, Random, 95% CI)	-0.94 [-3.33, 1.45]
4.3 Other underlying pathology	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Quality of life improvement	1	231	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.11]
5.1 AIDS	1	231	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.11]
6 Quality of life gain	1	63	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.23, 0.76]
6.1 AIDS	1	63	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.23, 0.76]

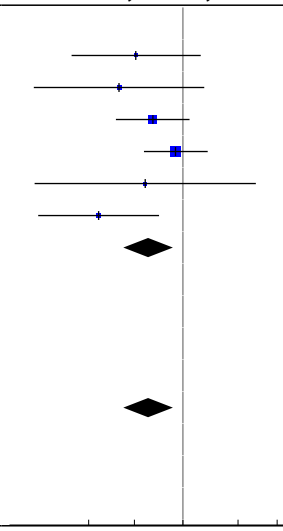
Analysis 3.1. Comparison 3 Megestrol acetate versus megestrol acetate (ITT), Outcome 1 Appetite improvement.

Study or subgroup	MA (low doses) n/N	MA (high doses) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Cancer					
Gebbia 1996	34/62	41/60		38.29%	0.8[0.6,1.07]
Schmoll 1992	22/34	15/29		21.03%	1.25[0.81,1.92]
Ulutin 2002	37/59	39/60		40.68%	0.96[0.74,1.26]
Subtotal (95% CI)	**155**	**149**		**100%**	**0.95[0.76,1.18]**
Total events: 93 (MA (low doses)), 95 (MA (high doses))					
Heterogeneity: Tau^2=0.01; Chi^2=2.92, df=2(P=0.23); I^2=31.55%					
Test for overall effect: Z=0.46(P=0.65)					
Total (95% CI)	**155**	**149**		**100%**	**0.95[0.76,1.18]**
Total events: 93 (MA (low doses)), 95 (MA (high doses))					
Heterogeneity: Tau^2=0.01; Chi^2=2.92, df=2(P=0.23); I^2=31.55%					
Test for overall effect: Z=0.46(P=0.65)					



Analysis 3.2. Comparison 3 Megestrol acetate versus megestrol acetate (ITT), Outcome 2 Weight improvement.

Study or subgroup	MA (low doses) n/N	MA (high doses) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Cancer					
Gebbia 1996	19/62	26/60		12.39%	0.71[0.44,1.14]
Heckmayr 1992	10/33	16/33		7.64%	0.63[0.33,1.17]
Loprinzi 1994	59/174	71/168		27.92%	0.8[0.61,1.05]
Sancho-Cuesta 1993	36/50	38/50		33.59%	0.95[0.75,1.2]
Schmoll 1992	8/34	9/29		4.72%	0.76[0.34,1.71]
Ulutin 2002	18/59	34/60		13.75%	0.54[0.35,0.84]
Subtotal (95% CI)	**412**	**400**		**100%**	**0.77[0.64,0.93]**
Total events: 150 (MA (low doses)), 194 (MA (high doses))					
Heterogeneity: Tau^2=0.01; Chi^2=6.48, df=5(P=0.26); I^2=22.87%					
Test for overall effect: Z=2.76(P=0.01)					
Total (95% CI)	**412**	**400**		**100%**	**0.77[0.64,0.93]**
Total events: 150 (MA (low doses)), 194 (MA (high doses))					
Heterogeneity: Tau^2=0.01; Chi^2=6.48, df=5(P=0.26); I^2=22.87%					
Test for overall effect: Z=2.76(P=0.01)					

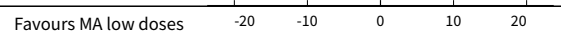


Analysis 3.3. Comparison 3 Megestrol acetate versus megestrol acetate (ITT), Outcome 3 Weight improvement 160 mg versus other higher doses.

Study or subgroup	MA (low doses) n/N	MA (high doses) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Cancer					
Gebbia 1996	19/62	26/60		22.74%	0.71[0.44,1.14]
Heckmayr 1992	10/33	16/33		16.58%	0.63[0.33,1.17]
Sancho-Cuesta 1993	36/50	38/50		36.51%	0.95[0.75,1.2]
Ulutin 2002	18/59	34/60		24.17%	0.54[0.35,0.84]
Subtotal (95% CI)	**204**	**203**		**100%**	**0.72[0.52,0.99]**
Total events: 83 (MA (low doses)), 114 (MA (high doses))					
Heterogeneity: Tau^2=0.06; Chi^2=7.01, df=3(P=0.07); I^2=57.18%					
Test for overall effect: Z=2(P=0.05)					
Total (95% CI)	**204**	**203**		**100%**	**0.72[0.52,0.99]**
Total events: 83 (MA (low doses)), 114 (MA (high doses))					
Heterogeneity: Tau^2=0.06; Chi^2=7.01, df=3(P=0.07); I^2=57.18%					
Test for overall effect: Z=2(P=0.05)					

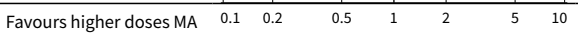
Analysis 3.4. Comparison 3 Megestrol acetate versus megestrol acetate (ITT), Outcome 4 Weight gain.

Study or subgroup	MA (low doses) N	MA (low doses) Mean(SD)	MA (high doses) N	MA (high doses) Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.4.1 Cancer							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.4.2 AIDS							
Von Roenn 1994	53	1.9 (4.3)	53	3.5 (4.3)		35.01%	-1.63[-3.26,0]
Von Roenn 1994	61	0.9 (4.6)	53	3.5 (4.3)		35.01%	-2.68[-4.31,-1.05]
Wanke 2007	32	5.4 (5.3)	31	3.5 (4)		29.98%	1.9[-0.43,4.23]
Subtotal ***	**146**		**137**			**100%**	**-0.94[-3.33,1.45]**
Heterogeneity: Tau^2=3.56; Chi^2=10.16, df=2(P=0.01); I^2=80.32%							
Test for overall effect: Z=0.77(P=0.44)							
3.4.3 Other underlying pathology							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**146**		**137**			**100%**	**-0.94[-3.33,1.45]**
Heterogeneity: Tau^2=3.56; Chi^2=10.16, df=2(P=0.01); I^2=80.32%							
Test for overall effect: Z=0.77(P=0.44)							
Test for subgroup differences: Not applicable							



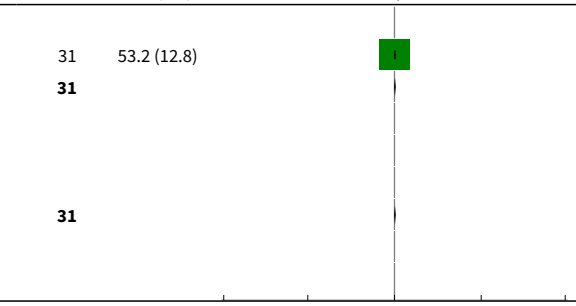
Analysis 3.5. Comparison 3 Megestrol acetate versus megestrol acetate (ITT), Outcome 5 Quality of life improvement.

Study or subgroup	MA (low doses) n/N	MA (high doses) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 AIDS					
Von Roenn 1994	57/156	34/75		100%	0.81[0.58,1.11]
Subtotal (95% CI)	**156**	**75**		**100%**	**0.81[0.58,1.11]**
Total events: 57 (MA (low doses)), 34 (MA (high doses))					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					
Total (95% CI)	**156**	**75**		**100%**	**0.81[0.58,1.11]**
Total events: 57 (MA (low doses)), 34 (MA (high doses))					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					



Analysis 3.6. Comparison 3 Megestrol acetate versus megestrol acetate (ITT), Outcome 6 Quality of life gain.

Study or subgroup	MA (low doses) N	MA (low doses) Mean(SD)	MA (high doses) N	MA (high doses) Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.6.1 AIDS							
Wanke 2007	32	56.2 (9.5)	31	53.2 (12.8)		100%	0.26[-0.23,0.76]
Subtotal ***	**32**		**31**			**100%**	**0.26[-0.23,0.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.04(P=0.3)							
Total ***	**32**		**31**			**100%**	**0.26[-0.23,0.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.04(P=0.3)							



Comparison 4. Safety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute decompensation of COPD or pulmonary exacerbation	4	271	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.72, 2.51]
1.1 High doses (=> 800 mg/d)	2	214	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.41, 5.83]
1.2 Low doses (< 800 mg/d)	2	57	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.65, 2.40]
2 Serious adverse events (SAE)	4	467	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.98, 4.47]
2.1 High doses (=> 800 mg/d)	1	145	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.31, 2.46]
2.2 Low doses (< 800 mg/d)	3	322	Risk Ratio (M-H, Fixed, 95% CI)	4.65 [1.33, 16.29]
3 Any adverse event	13	1241	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.07, 1.36]
3.1 High doses (=> 800 mg/d)	5	347	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.01, 1.83]
3.2 Low doses (< 800 mg/d)	9	894	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.01, 1.32]
4 Abdominal pain	3	535	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.89, 3.06]
4.1 High doses (=> 800 mg/d)	2	475	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.89, 3.20]
4.2 Low doses (< 800 mg/d)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 16.31]
5 Abnormal appetite	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.73]
5.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Low doses (< 800 mg/d)	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.73]
6 Amenorrhoea/irregular menses	5	504	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.45, 2.09]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 High doses (=> 800 mg/d)	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.53, 5.75]
6.2 Low doses (< 800 mg/d)	3	338	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.22, 1.77]
7 Bowel obstruction	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.70]
7.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Low doses (< 800 mg/d)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.70]
8 Constipation	2	167	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.20, 16.73]
8.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Low doses (< 800 mg/d)	2	167	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.20, 16.73]
9 Chest pain	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
9.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Low doses (<800 mg/d)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
10 Confusion	2	592	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.62, 1.28]
10.1 High doses(=> 800 mg /d)	1	311	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.58, 1.33]
10.2 Low doses (< 800 mg/d)	1	281	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.46, 1.92]
11 Dyspnoea	7	858	Risk Ratio (M-H, Fixed, 95% CI)	2.23 [1.01, 4.93]
11.1 High doses (=> 800 mg/d)	4	379	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.37, 5.16]
11.2 Low doses (< 800 mg/d)	4	479	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [1.02, 7.67]
12 Depression	2	86	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.27, 22.18]
12.1 High doses (=> 800 mg/d)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.12, 65.41]
12.2 Low doses (< 800 mg/d)	1	17	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.10, 46.92]
13 Deaths	11	1367	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.04, 1.94]
13.1 High doses (=> 800 mg/d)	5	726	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.08, 2.57]
13.2 Low doses (< 800 mg/d)	7	641	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.77, 1.86]
14 Diarrhoea	4	374	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.35, 3.02]
14.1 High doses (=> 800 mg/d)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.29, 5.22]
14.2 Low doses (< 800 mg/d)	3	274	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.16, 4.26]
15 Drowsiness	1	311	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.66, 1.23]

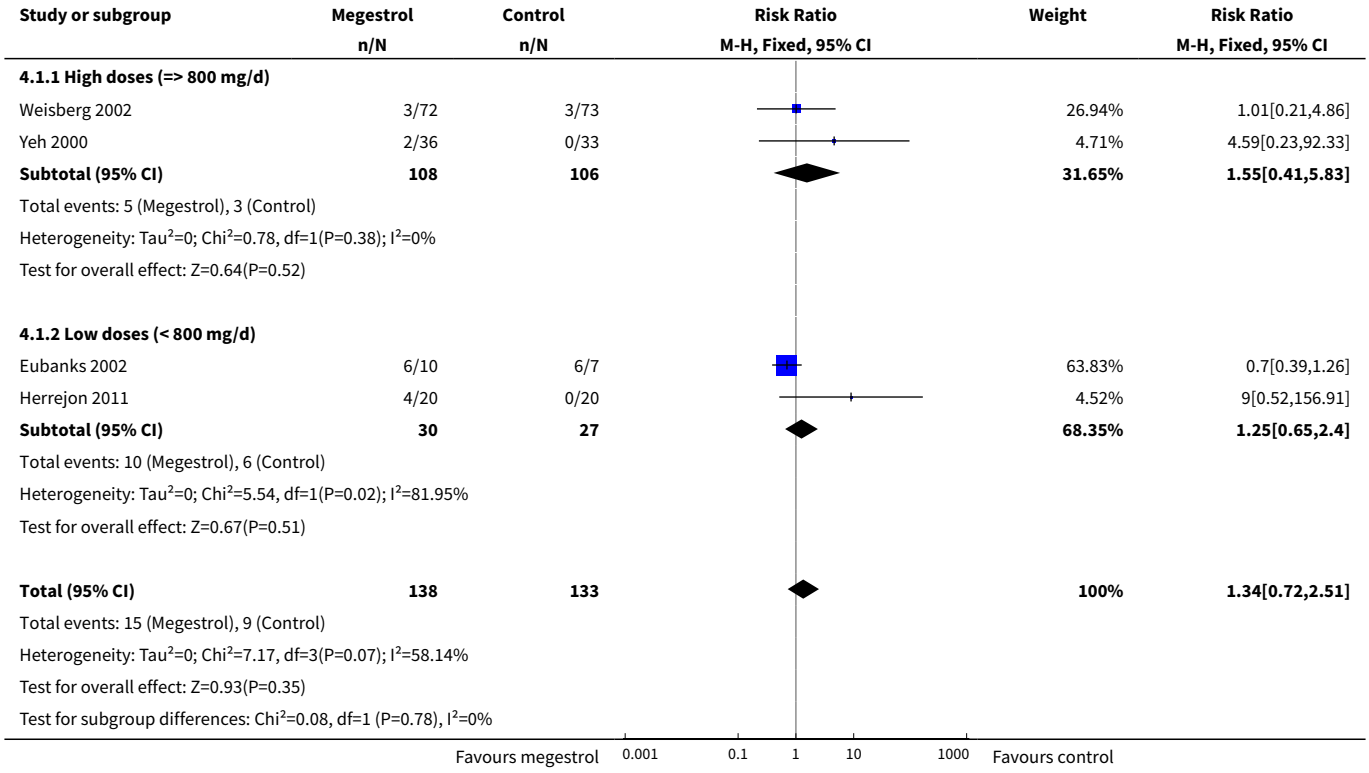
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
15.1 High doses (=> 800 mg/d)	1	311	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.66, 1.23]
15.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Elevated transaminase levels	2	64	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.59]
16.1 High doses (=> 800 mg/d)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.54]
16.2 Low doses (< 800 mg/d)	1	24	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 67.06]
17 Glucose intolerance	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.16, 4.80]
17.1 High doses (=> 800 mg/d)	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.16, 4.80]
17.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Hallucinations/psychosis	2	113	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.08, 3.83]
18.1 High doses (=> 800 mg/d)	2	113	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.08, 3.83]
18.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Headaches	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
19.1 High doses (=> 800 mg/d)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
19.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Hyperphagia	1	10	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.42, 116.40]
20.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Low doses (< 800 mg/d)	1	10	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.42, 116.40]
21 Heart burn	3	517	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.37, 1.35]
21.1 High doses (=> 800 mg/d)	2	475	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.38, 1.43]
21.2 Low doses (< 800 mg/d)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.74]
22 Heart failure	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 6.53]
22.1 High doses (=> 800 mg/d)	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 6.53]
22.2 Low doses (<800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Hypertension	3	289	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.14, 2.91]
23.1 High doses(=> 800 mg /d)	3	240	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.14, 2.91]
23.2 Low doses (< 800 mg/d)	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Impotence	13	2071	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.78, 3.75]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
24.1 High doses (=> 800 mg/d)	8	1346	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [1.63, 3.81]
24.2 Low doses (< 800 mg/d)	6	725	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [1.33, 6.26]
25 Infections	5	885	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.64, 1.39]
25.1 High doses (=> 800 mg/d)	4	669	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
25.2 Low doses (< 800 mg/d)	2	216	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.39, 2.96]
26 Inappropriate behaviour	1	311	Risk Ratio (M-H, Fixed, 95% CI)	4.78 [0.56, 40.44]
26.1 High doses (=> 800 mg/d)	1	311	Risk Ratio (M-H, Fixed, 95% CI)	4.78 [0.56, 40.44]
26.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Insomnia	3	492	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [0.87, 15.77]
27.1 High doses (=> 800 mg/d)	2	475	Risk Ratio (M-H, Fixed, 95% CI)	4.51 [0.58, 35.31]
27.2 Low doses (< 800 mg/d)	1	17	Risk Ratio (M-H, Fixed, 95% CI)	2.8 [0.39, 20.02]
28 Loss of co-ordination	1	311	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.62, 1.75]
28.1 High doses (=> 800 mg/d)	1	311	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.62, 1.75]
28.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Nausea/vomiting	13	1645	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.45, 0.74]
29.1 High doses (=> 800 mg/d)	6	997	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.37, 0.72]
29.2 Low doses (< 800 mg/d)	8	648	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.46, 1.00]
30 Neoplasma	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.06, 14.07]
30.1 High doses (=> 800 mg/d)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.06, 14.07]
30.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Oedema	12	2182	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.07, 1.72]
31.1 High doses (=> 800 mg/d)	8	1285	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.04, 1.81]
31.2 Low doses (< 800 mg/d)	6	897	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.84, 2.09]
32 Pneumonia	4	296	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.51, 6.42]
32.1 High doses (=> 800 mg/d)	2	214	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.28, 6.54]
32.2 Low doses (< 800 mg/d)	2	82	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 27.71]
33 Pruritus	2	272	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.81]

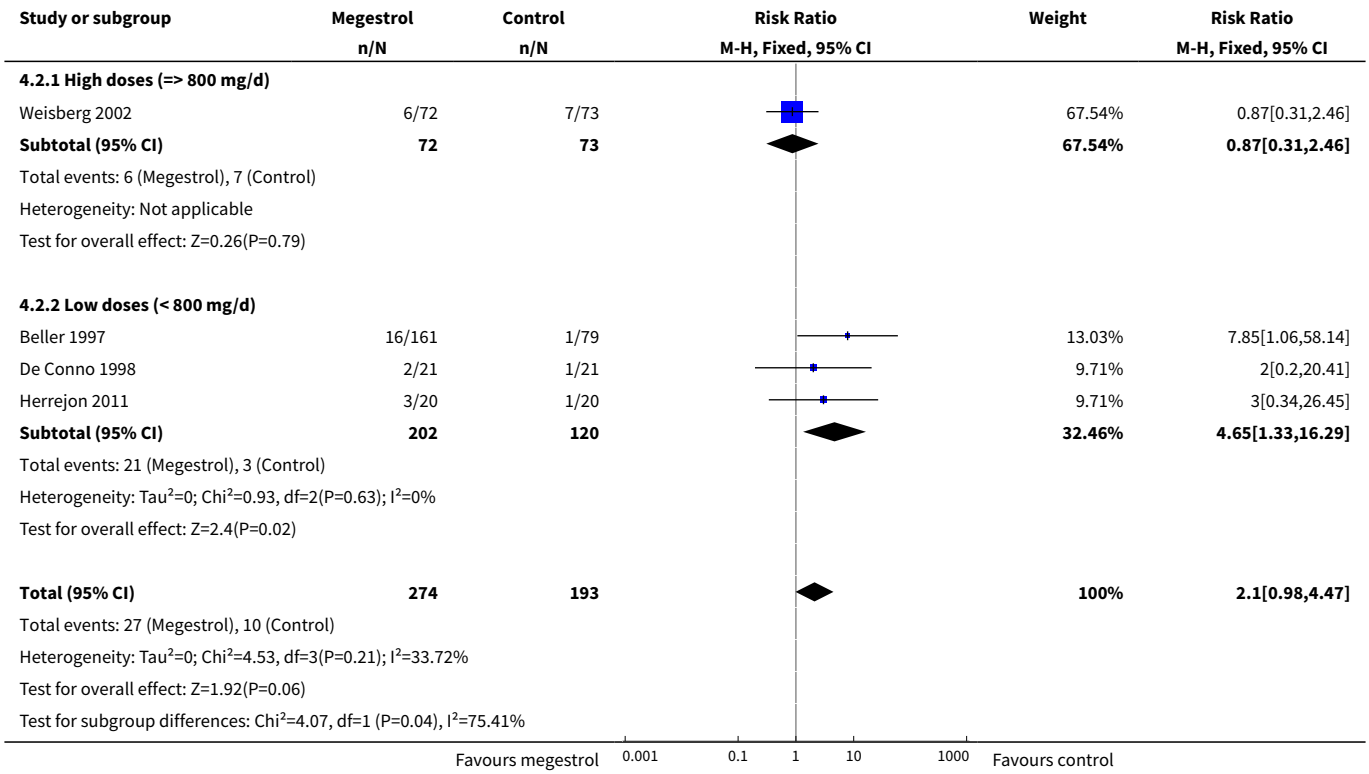
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
33.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.2 Low doses (< 800 mg/d)	2	272	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.81]
34 Pyrosis	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.40, 6.55]
34.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.2 Low doses (< 800 mg/d)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.40, 6.55]
35 Pulmonary embolism	1	240	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [0.12, 50.83]
35.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.2 Low doses (< 800 mg/d)	1	240	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [0.12, 50.83]
36 Respiratory failure	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.74]
36.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.2 Low doses (< 800 mg/d)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.74]
37 Other adverse events	3	254	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.60, 3.76]
37.1 High doses (=> 800 mg/d)	3	254	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.60, 3.76]
37.2 Low doses (< 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38 Skin disorder (includes vesiculobul-lous rash)	3	157	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.21, 3.36]
38.1 High doses (=> 800 mg/d)	2	140	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.22, 11.88]
38.2 Low doses (< 800 mg/d)	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.15]
39 Sweating	3	109	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.54, 18.35]
39.1 High doses (=> 800 mg/d)	2	92	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.31, 26.58]
39.2 Low doses (< 800 mg/d)	1	17	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [0.20, 65.86]
40 Swelling legs or abdominal	3	756	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.39]
40.1 High doses (=> 800 mg/d)	2	475	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.23, 1.68]
40.2 Low doses (< 800 mg/d)	1	281	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.79, 1.54]
41 Stroke	2	183	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.24, 5.64]
41.1 High doses (=> 800 mg/d)	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.10, 5.22]
41.2 Low doses (< 800 mg/d)	1	49	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.14, 53.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
42 Thromboembolic phenomena including thrombophlebitis	12	1604	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.07, 3.18]
42.1 High doses (=> 800 mg/d)	6	792	Risk Ratio (M-H, Random, 95% CI)	2.35 [0.93, 5.94]
42.2 Low doses (< 800 mg/d)	7	812	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.82, 3.18]
43 Testicular shrinkage	1	10	Risk Ratio (M-H, Fixed, 95% CI)	4.2 [0.21, 83.33]
43.1 High doses (=> 800 mg/d)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
43.2 Low doses (< 800 mg/d)	1	10	Risk Ratio (M-H, Fixed, 95% CI)	4.2 [0.21, 83.33]
44 Withdrawals	16	1339	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.06]
44.1 High doses (=> 800 mg/d)	6	818	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.80, 1.06]
44.2 Low doses (< 800 mg/d)	10	521	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.75, 1.28]

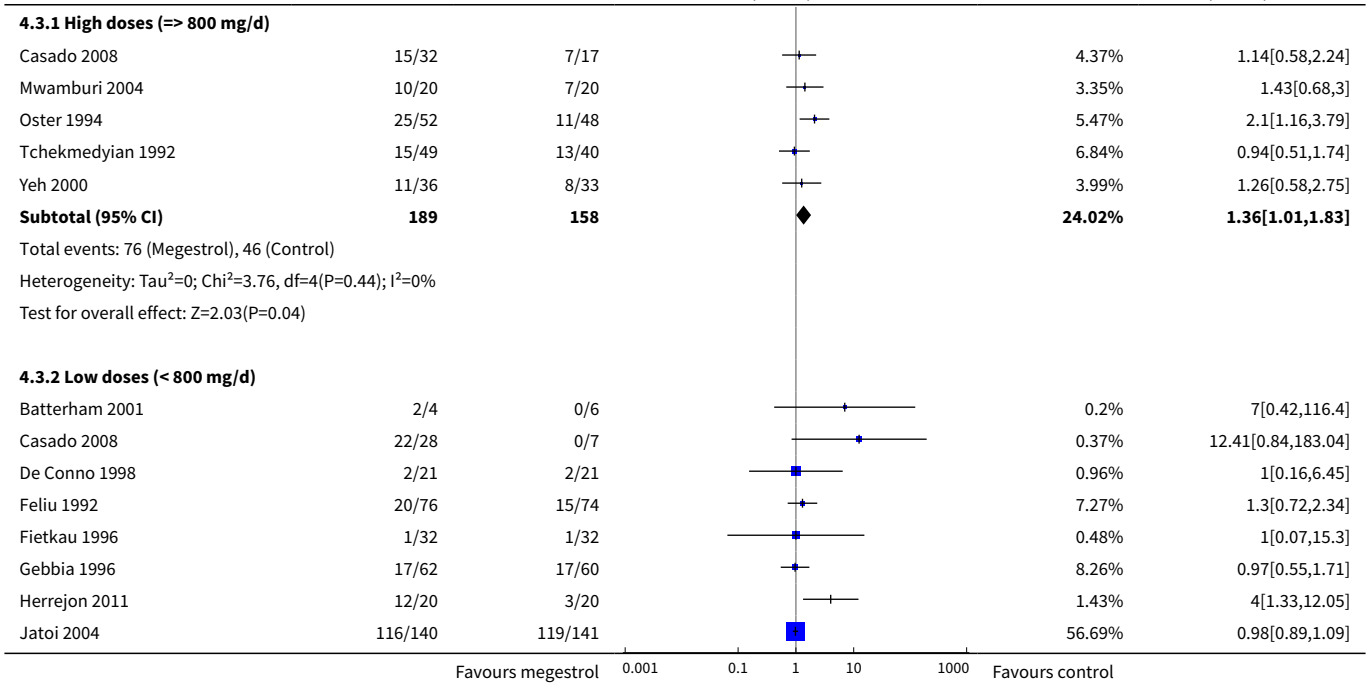
Analysis 4.1. Comparison 4 Safety, Outcome 1 Acute decompensation of COPD or pulmonary exacerbation.

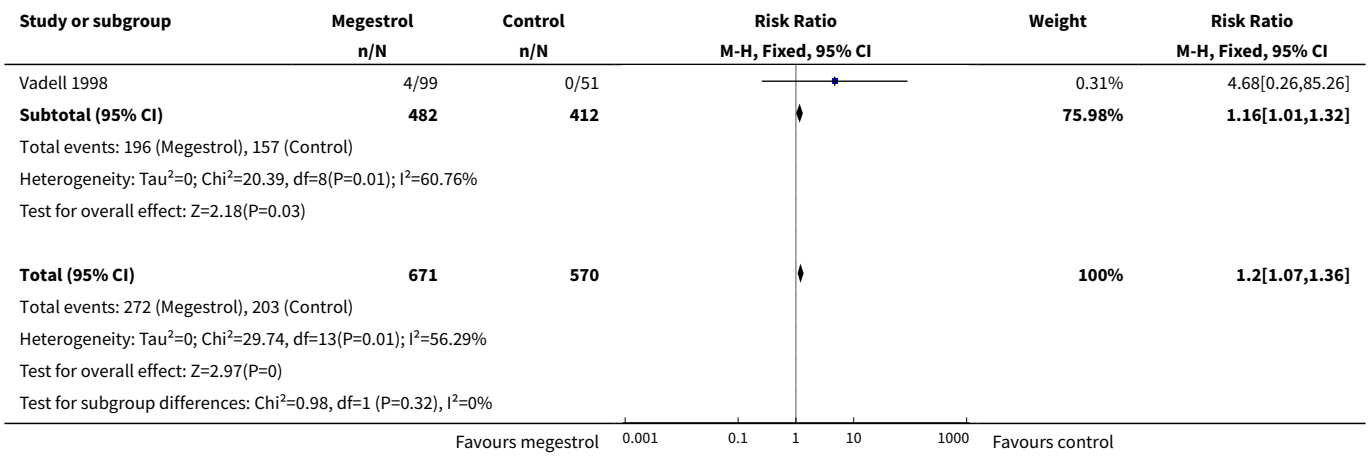


Analysis 4.2. Comparison 4 Safety, Outcome 2 Serious adverse events (SAE).

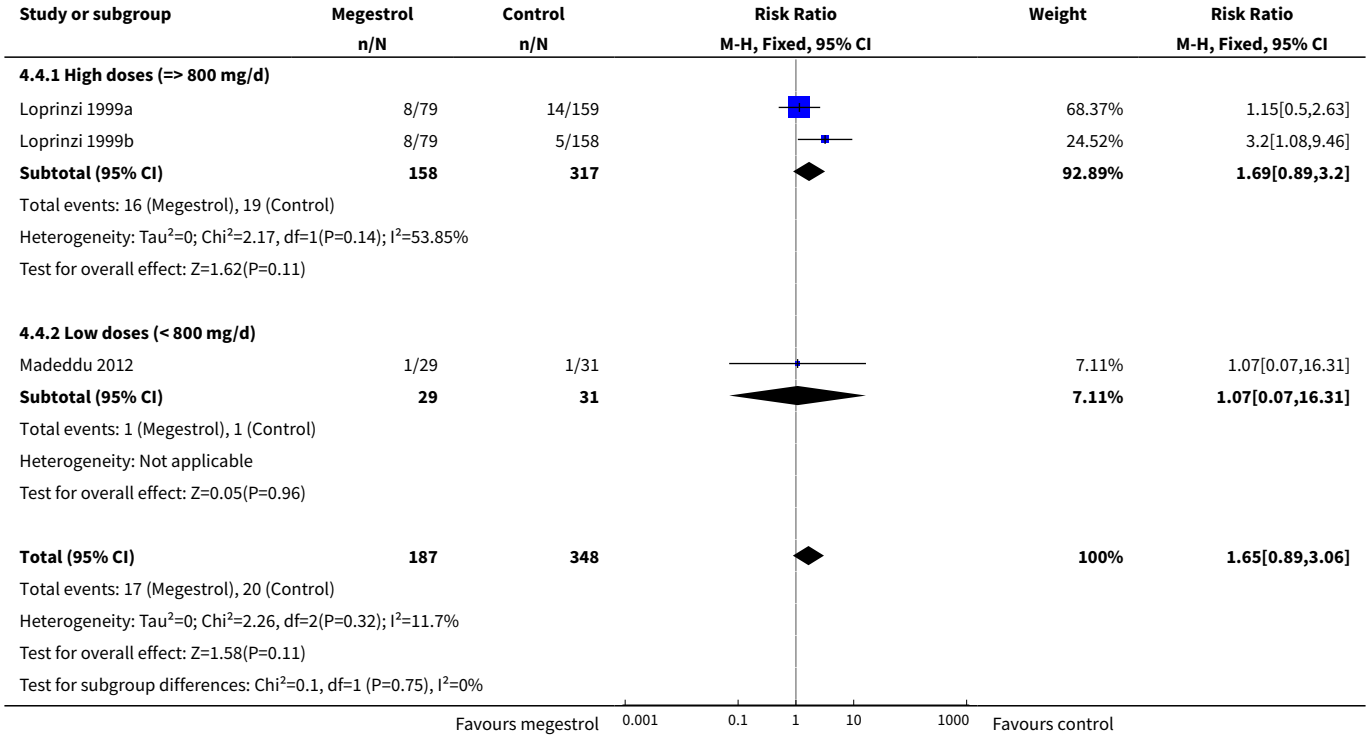


Analysis 4.3. Comparison 4 Safety, Outcome 3 Any adverse event.

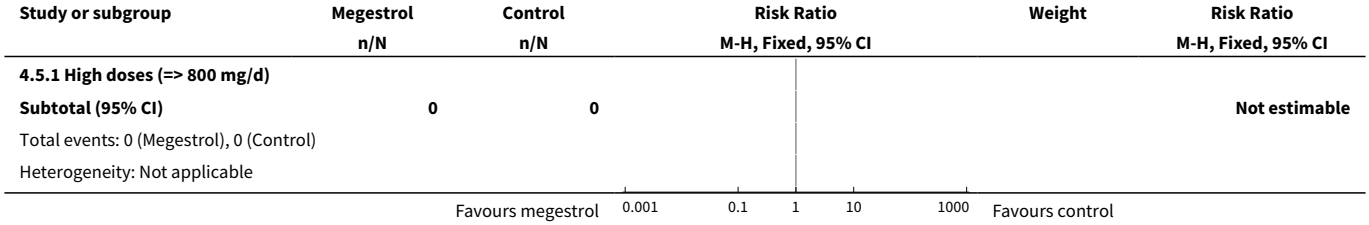


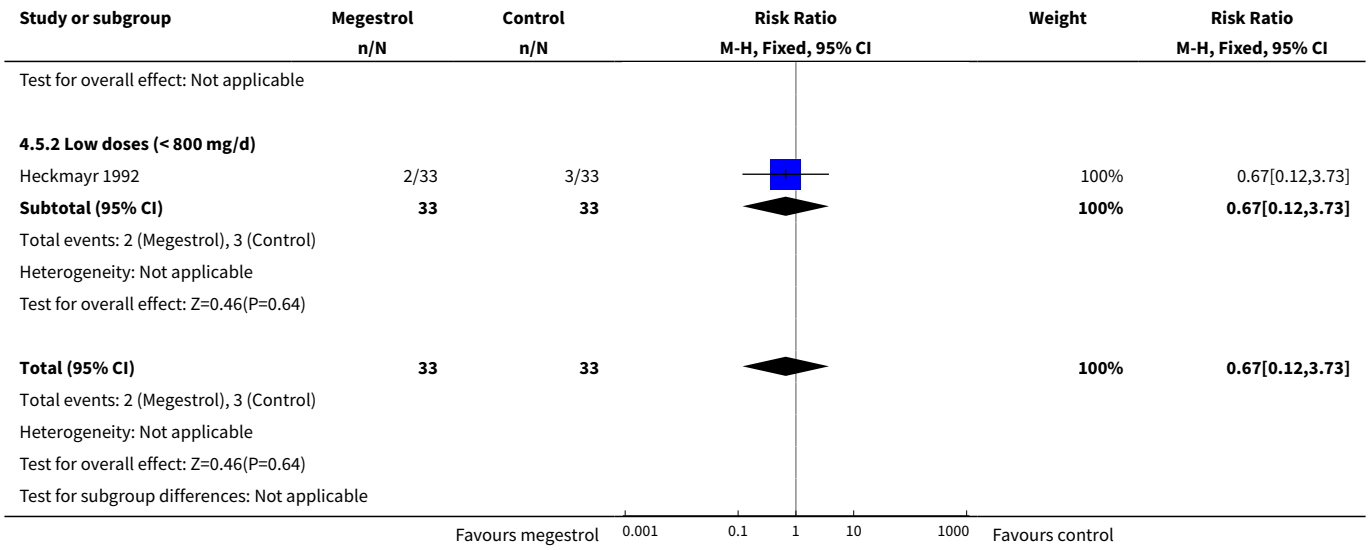


Analysis 4.4. Comparison 4 Safety, Outcome 4 Abdominal pain.

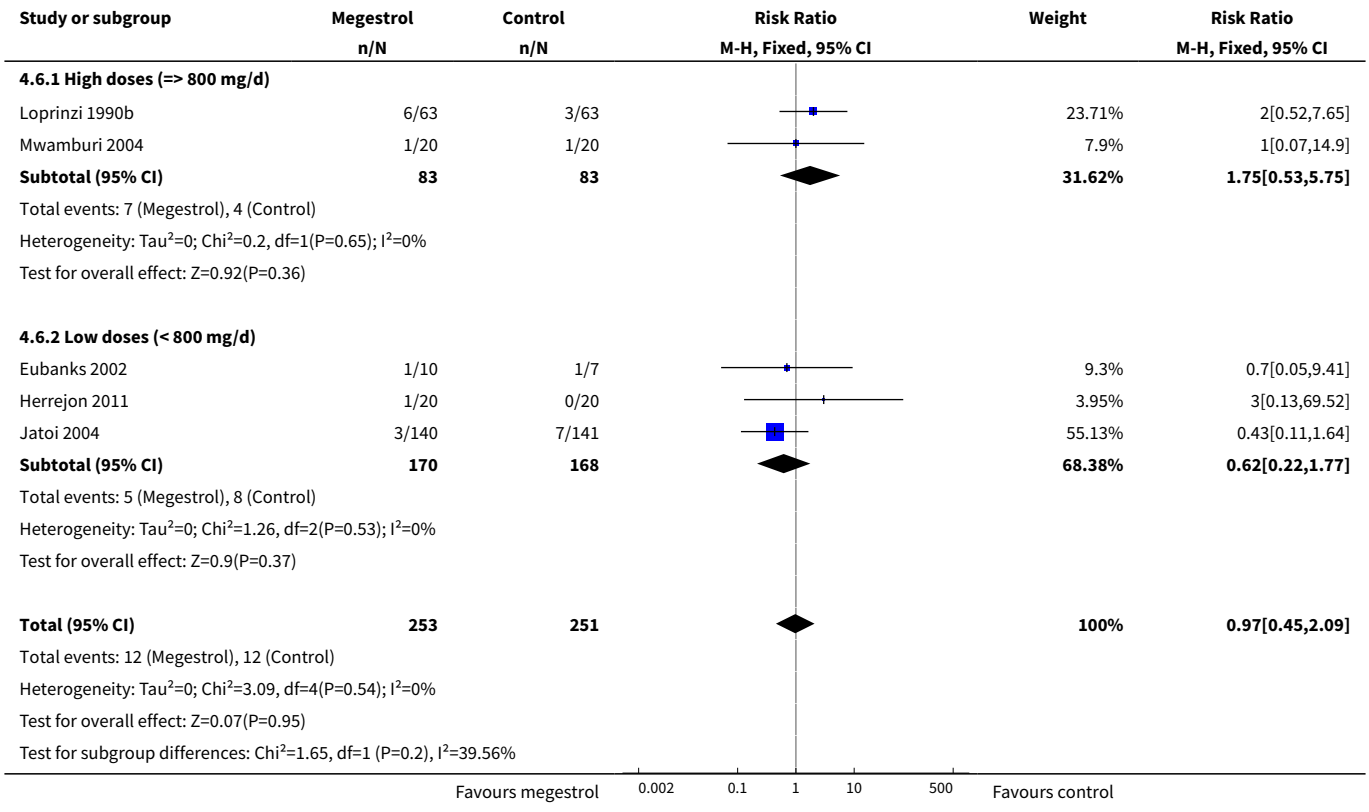


Analysis 4.5. Comparison 4 Safety, Outcome 5 Abnormal appetite.



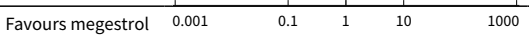


Analysis 4.6. Comparison 4 Safety, Outcome 6 Amenorrhoea/irregular menses.



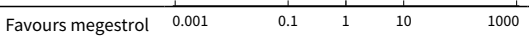
Analysis 4.7. Comparison 4 Safety, Outcome 7 Bowel obstruction.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.7.2 Low doses (< 800 mg/d)					
De Conno 1998	1/21	0/21		100%	3[0.13,69.7]
Subtotal (95% CI)	**21**	**21**		**100%**	**3[0.13,69.7]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.49)					
Total (95% CI)	**21**	**21**		**100%**	**3[0.13,69.7]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.49)					
Test for subgroup differences: Not applicable					



Analysis 4.8. Comparison 4 Safety, Outcome 8 Constipation.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.8.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.8.2 Low doses (< 800 mg/d)					
Eubanks 2002	1/10	0/7		46.81%	2.18[0.1,46.92]
Vadell 1998	1/99	0/51		53.19%	1.56[0.06,37.63]
Subtotal (95% CI)	**109**	**58**		**100%**	**1.85[0.2,16.73]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					
Total (95% CI)	**109**	**58**		**100%**	**1.85[0.2,16.73]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Not applicable					

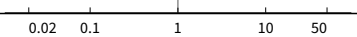


Analysis 4.9. Comparison 4 Safety, Outcome 9 Chest pain.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.9.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.9.2 Low doses (<800 mg/d)					
Herrejon 2011	1/20	0/20		100%	3[0.13,69.52]
Subtotal (95% CI)	**20**	**20**		**100%**	**3[0.13,69.52]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
Total (95% CI)	**20**	**20**		**100%**	**3[0.13,69.52]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
Test for subgroup differences: Not applicable					

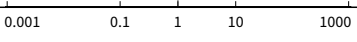
Analysis 4.10. Comparison 4 Safety, Outcome 10 Confusion.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.10.1 High doses(=> 800 mg /d)					
Jatoi 2002	33/159	36/152		72.52%	0.88[0.58,1.33]
Subtotal (95% CI)	**159**	**152**		**72.52%**	**0.88[0.58,1.33]**
Total events: 33 (Megestrol), 36 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.53)					
4.10.2 Low doses (< 800 mg/d)					
Jatoi 2004	13/140	14/141		27.48%	0.94[0.46,1.92]
Subtotal (95% CI)	**140**	**141**		**27.48%**	**0.94[0.46,1.92]**
Total events: 13 (Megestrol), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.18(P=0.85)					
Total (95% CI)	**299**	**293**		**100%**	**0.89[0.62,1.28]**
Total events: 46 (Megestrol), 50 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=0.62(P=0.54)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					



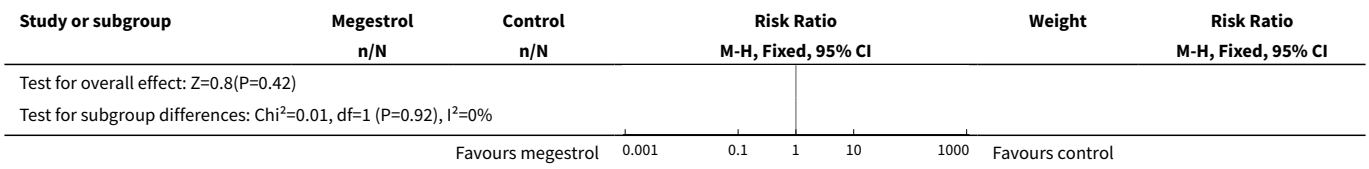
Analysis 4.11. Comparison 4 Safety, Outcome 11 Dyspnoea.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.11.1 High doses (=> 800 mg/d)					
Casado 2008	0/28	0/17			Not estimable
Oster 1994	1/52	0/48		5.62%	2.77[0.12,66.49]
Tchekmedyian 1992	3/49	2/40		23.82%	1.22[0.21,6.97]
Weisberg 2002	1/72	1/73		10.74%	1.01[0.06,15.9]
Subtotal (95% CI)	**201**	**178**		**40.19%**	**1.38[0.37,5.16]**
Total events: 5 (Megestrol), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=2(P=0.88); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
4.11.2 Low doses (< 800 mg/d)					
Beller 1997	10/161	1/79		14.51%	4.91[0.64,37.66]
Casado 2008	3/32	0/17		7%	3.82[0.21,69.88]
Feliu 1992	5/76	3/74		32.89%	1.62[0.4,6.55]
Herrejon 2011	1/20	0/20		5.41%	3[0.13,69.52]
Subtotal (95% CI)	**289**	**190**		**59.81%**	**2.8[1.02,7.67]**
Total events: 19 (Megestrol), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=3(P=0.82); I^2=0%					
Test for overall effect: Z=2.01(P=0.04)					
Total (95% CI)	**490**	**368**		**100%**	**2.23[1.01,4.93]**
Total events: 24 (Megestrol), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.73, df=6(P=0.94); I^2=0%					
Test for overall effect: Z=1.98(P=0.05)					
Test for subgroup differences: Chi^2=0.69, df=1 (P=0.4), I^2=0%					

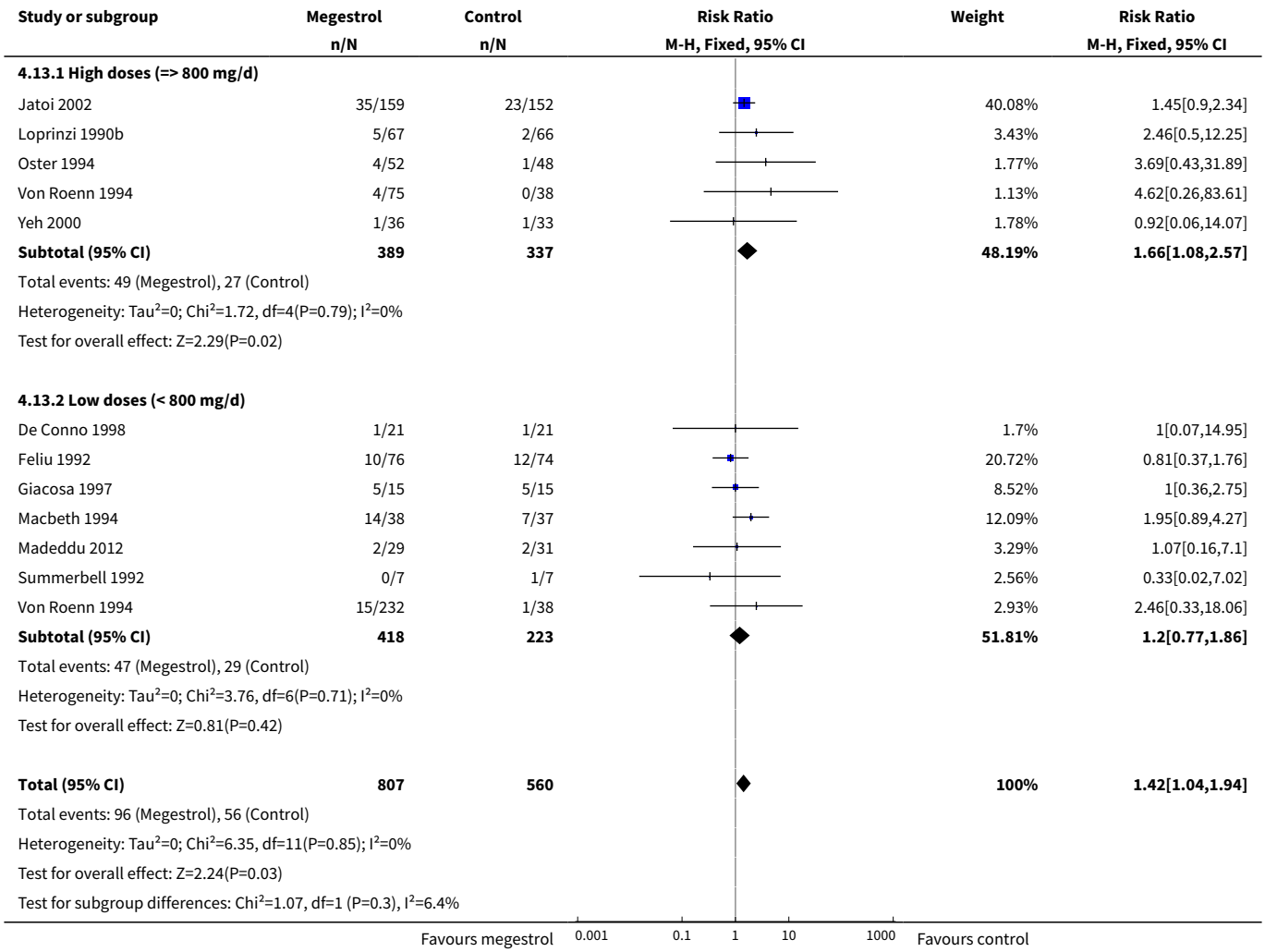


Analysis 4.12. Comparison 4 Safety, Outcome 12 Depression.

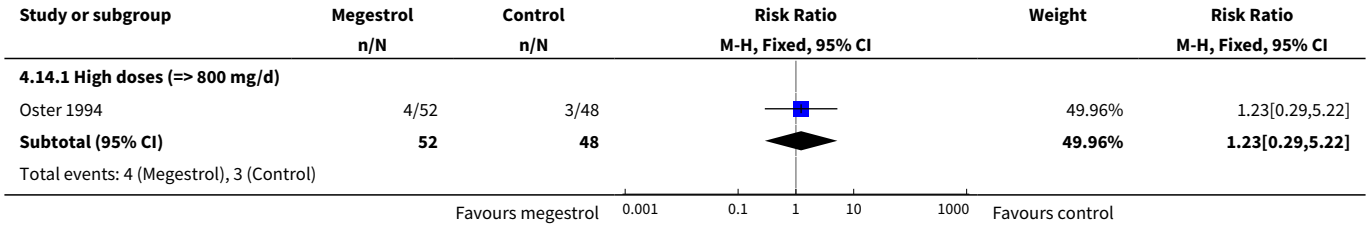
Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.12.1 High doses (=> 800 mg/d)					
Yeh 2000	1/36	0/33		47.37%	2.76[0.12,65.41]
Subtotal (95% CI)	**36**	**33**		**47.37%**	**2.76[0.12,65.41]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
4.12.2 Low doses (< 800 mg/d)					
Eubanks 2002	1/10	0/7		52.63%	2.18[0.1,46.92]
Subtotal (95% CI)	**10**	**7**		**52.63%**	**2.18[0.1,46.92]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.5(P=0.62)					
Total (95% CI)	**46**	**40**		**100%**	**2.45[0.27,22.18]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					

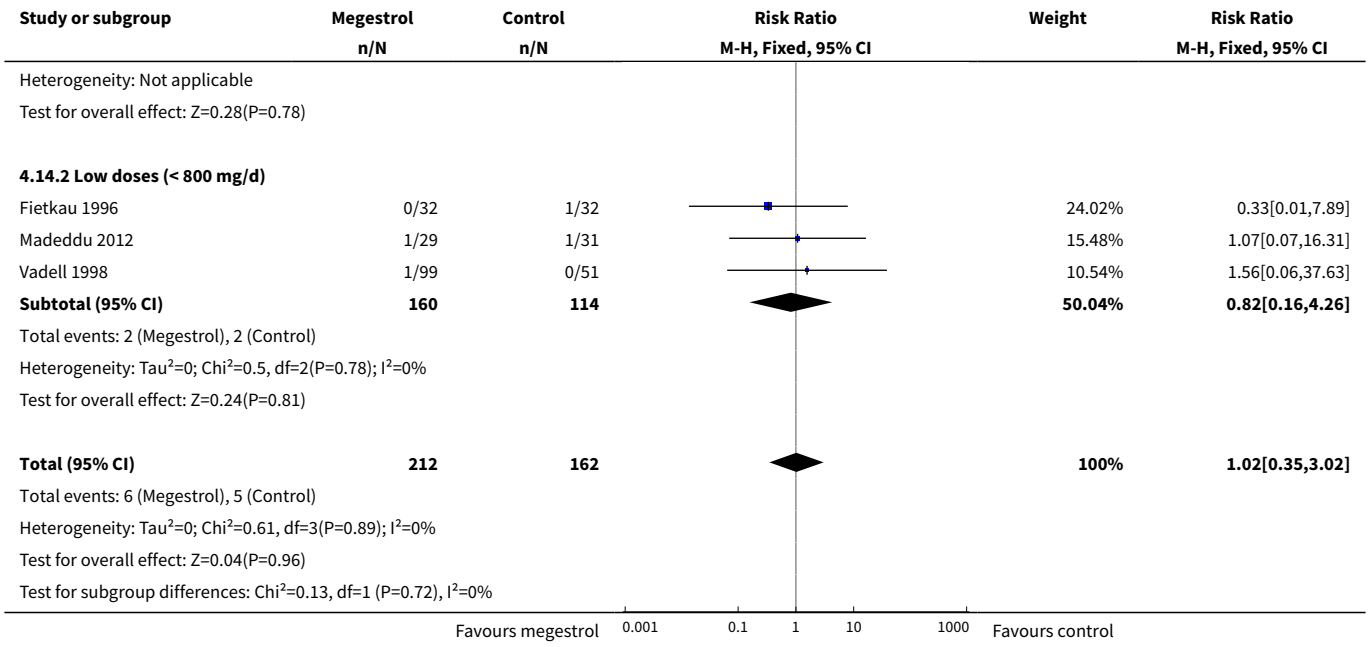


Analysis 4.13. Comparison 4 Safety, Outcome 13 Deaths.

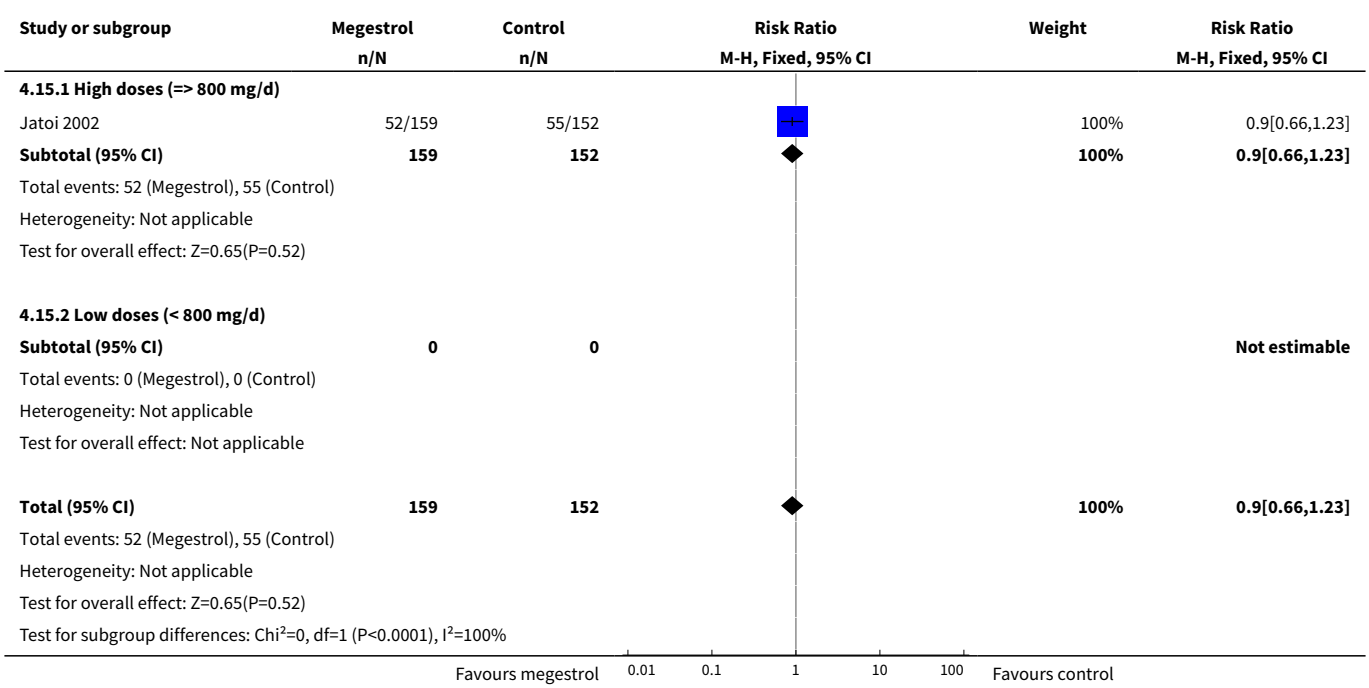


Analysis 4.14. Comparison 4 Safety, Outcome 14 Diarrhoea.



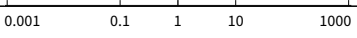


Analysis 4.15. Comparison 4 Safety, Outcome 15 Drowsiness.



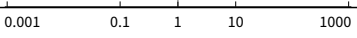
Analysis 4.16. Comparison 4 Safety, Outcome 16 Elevated transaminase levels.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.16.1 High doses (=> 800 mg/d)					
Mwamburi 2004	0/20	5/20		91.67%	0.09[0.01,1.54]
Subtotal (95% CI)	**20**	**20**		**91.67%**	**0.09[0.01,1.54]**
Total events: 0 (Megestrol), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					
4.16.2 Low doses (< 800 mg/d)					
Timpone 1997	1/12	0/12		8.33%	3[0.13,67.06]
Subtotal (95% CI)	**12**	**12**		**8.33%**	**3[0.13,67.06]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
Total (95% CI)	**32**	**32**		**100%**	**0.33[0.07,1.59]**
Total events: 1 (Megestrol), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.73, df=1(P=0.1); I^2=63.37%					
Test for overall effect: Z=1.38(P=0.17)					
Test for subgroup differences: Chi^2=2.66, df=1 (P=0.1), I^2=62.38%					



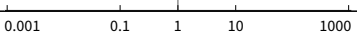
Analysis 4.17. Comparison 4 Safety, Outcome 17 Glucose intolerance.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.17.1 High doses (=> 800 mg/d)					
Mwamburi 2004	1/20	0/20		18.5%	3[0.13,69.52]
Tchekmedyian 1992	1/49	2/40		81.5%	0.41[0.04,4.34]
Subtotal (95% CI)	**69**	**60**		**100%**	**0.89[0.16,4.8]**
Total events: 2 (Megestrol), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.99, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					
4.17.2 Low doses (< 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**69**	**60**		**100%**	**0.89[0.16,4.8]**
Total events: 2 (Megestrol), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.99, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					
Test for subgroup differences: Chi^2=0, df=1 (P<0.0001), I^2=100%					



Analysis 4.18. Comparison 4 Safety, Outcome 18 Hallucinations/psychosis.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.18.1 High doses (=> 800 mg/d)					
Tchekmedyian 1992	0/49	1/40		62.24%	0.27[0.01,6.53]
Timpone 1997	1/12	1/12		37.76%	1[0.07,14.21]
Subtotal (95% CI)	**61**	**52**		**100%**	**0.55[0.08,3.83]**
Total events: 1 (Megestrol), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.38, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
4.18.2 Low doses (< 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**61**	**52**		**100%**	**0.55[0.08,3.83]**
Total events: 1 (Megestrol), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.38, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
Test for subgroup differences: Not applicable					



Analysis 4.19. Comparison 4 Safety, Outcome 19 Headaches.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.19.1 High doses (=> 800 mg/d)					
Mwamburi 2004	1/20	0/20		100%	3[0.13,69.52]
Subtotal (95% CI)	**20**	**20**		**100%**	**3[0.13,69.52]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
4.19.2 Low doses (< 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**20**	**20**		**100%**	**3[0.13,69.52]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
Test for subgroup differences: Not applicable					

Analysis 4.20. Comparison 4 Safety, Outcome 20 Hyperphagia.

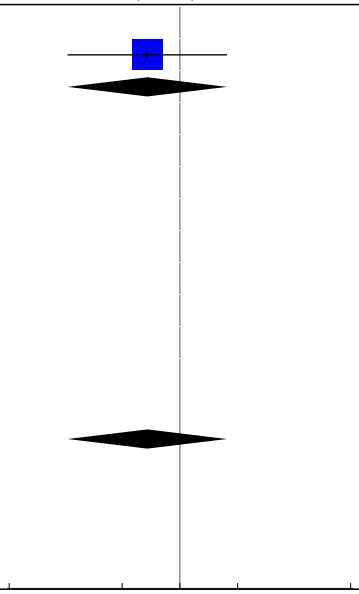
Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.20.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.20.2 Low doses (< 800 mg/d)					
Batterham 2001	2/4	0/6		100%	7[0.42,116.4]
Subtotal (95% CI)	**4**	**6**		**100%**	**7[0.42,116.4]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.36(P=0.17)					
Total (95% CI)	**4**	**6**		**100%**	**7[0.42,116.4]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.36(P=0.17)					
Test for subgroup differences: Not applicable					

Analysis 4.21. Comparison 4 Safety, Outcome 21 Heart burn.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.21.1 High doses (=> 800 mg/d)					
Loprinzi 1999a	5/79	22/159		68.13%	0.46[0.18,1.16]
Loprinzi 1999b	6/79	8/158		24.88%	1.5[0.54,4.17]
Subtotal (95% CI)	**158**	**317**		**93%**	**0.74[0.38,1.43]**
Total events: 11 (Megestrol), 30 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.86, df=1(P=0.09); I^2=65%					
Test for overall effect: Z=0.9(P=0.37)					
4.21.2 Low doses (< 800 mg/d)					
De Conno 1998	0/21	1/21		7%	0.33[0.01,7.74]
Subtotal (95% CI)	**21**	**21**		**7%**	**0.33[0.01,7.74]**
Total events: 0 (Megestrol), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.49)					
Total (95% CI)	**179**	**338**		**100%**	**0.71[0.37,1.35]**
Total events: 11 (Megestrol), 31 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.13, df=2(P=0.21); I^2=36.1%					
Test for overall effect: Z=1.04(P=0.3)					
Test for subgroup differences: Chi^2=0.23, df=1 (P=0.63), I^2=0%					

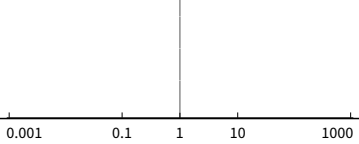
Analysis 4.22. Comparison 4 Safety, Outcome 22 Heart failure.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.22.1 High doses (=> 800 mg/d)					
Tchekmedyian 1992	0/49	1/40		100%	0.27[0.01,6.53]
Subtotal (95% CI)	**49**	**40**		**100%**	**0.27[0.01,6.53]**
Total events: 0 (Megestrol), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					
4.22.2 Low doses (<800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**49**	**40**		**100%**	**0.27[0.01,6.53]**
Total events: 0 (Megestrol), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					
Test for subgroup differences: Not applicable					



Analysis 4.23. Comparison 4 Safety, Outcome 23 Hypertension.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.23.1 High doses(=> 800 mg /d)					
Casado 2008	1/28	0/17		14.76%	1.86[0.08,43.28]
Loprinzi 1990b	1/63	2/63		47.84%	0.5[0.05,5.38]
Yeh 2000	0/36	1/33		37.4%	0.31[0.01,7.27]
Subtotal (95% CI)	**127**	**113**		**100%**	**0.63[0.14,2.91]**
Total events: 2 (Megestrol), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.69, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=0.59(P=0.55)					
4.23.2 Low doses (< 800 mg/d)					
Casado 2008	0/32	0/17			Not estimable
Subtotal (95% CI)	**32**	**17**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**159**	**130**		**100%**	**0.63[0.14,2.91]**
Total events: 2 (Megestrol), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.69, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=0.59(P=0.55)					
Test for subgroup differences: Not applicable					

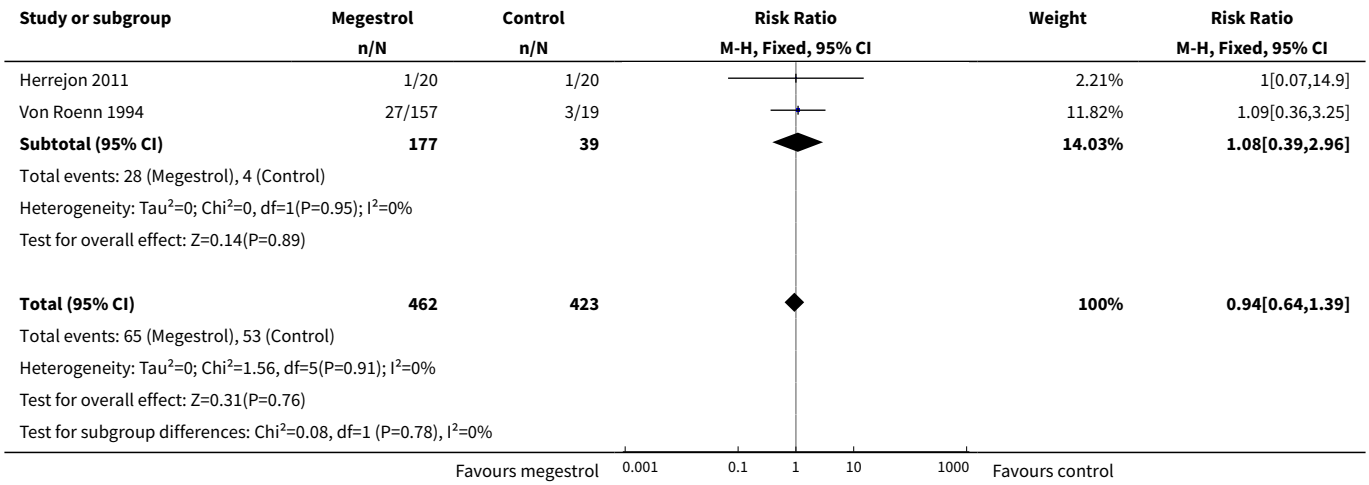


Analysis 4.24. Comparison 4 Safety, Outcome 24 Impotence.

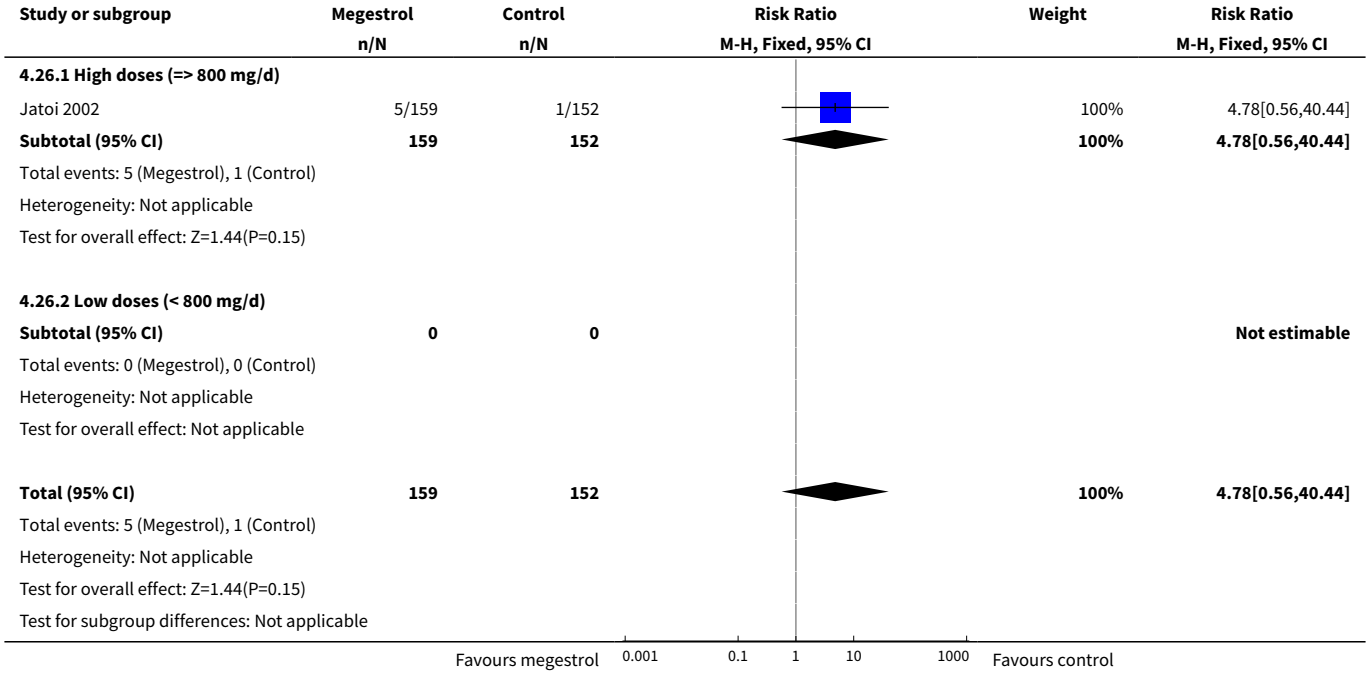
Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.24.1 High doses (=> 800 mg/d)					
Jatoi 2002	29/159	6/152		17.17%	4.62[1.97,10.82]
Loprinzi 1990b	6/63	3/63		8.39%	2[0.52,7.65]
Loprinzi 1999a	10/79	11/159		20.43%	1.83[0.81,4.12]
Loprinzi 1999b	9/79	13/158		24.25%	1.38[0.62,3.1]
Mwamburi 2004	1/20	0/20		1.4%	3[0.13,69.52]
Oster 1994	2/52	0/48		1.45%	4.62[0.23,93.91]
Tchekmedyian 1992	1/49	0/40		1.54%	2.46[0.1,58.79]
Von Roenn 1994	9/167	0/38		2.27%	4.41[0.26,74.18]
Subtotal (95% CI)	**668**	**678**		**76.91%**	**2.49[1.63,3.81]**
Total events: 67 (Megestrol), 33 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.06, df=7(P=0.65); I^2=0%					
Test for overall effect: Z=4.22(P<0.0001)					
4.24.2 Low doses (< 800 mg/d)					
Casado 2008	1/32	0/17		1.81%	1.64[0.07,38.14]
Fietkau 1996	1/32	0/32		1.4%	3[0.13,71]
Gebbia 1996	1/62	0/60		1.42%	2.9[0.12,69.93]
Jatoi 2004	13/140	4/141		11.15%	3.27[1.09,9.79]
Summerbell 1992	4/7	1/7		2.8%	4[0.58,27.41]
Von Roenn 1994	7/157	1/38		4.51%	1.69[0.21,13.36]
Subtotal (95% CI)	**430**	**295**		**23.09%**	**2.89[1.33,6.26]**
Total events: 27 (Megestrol), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=5(P=0.99); I^2=0%					
Test for overall effect: Z=2.68(P=0.01)					
Total (95% CI)	**1098**	**973**		**100%**	**2.58[1.78,3.75]**
Total events: 94 (Megestrol), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.85, df=13(P=0.95); I^2=0%					
Test for overall effect: Z=5(P<0.0001)					
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.75), I^2=0%					

Analysis 4.25. Comparison 4 Safety, Outcome 25 Infections.

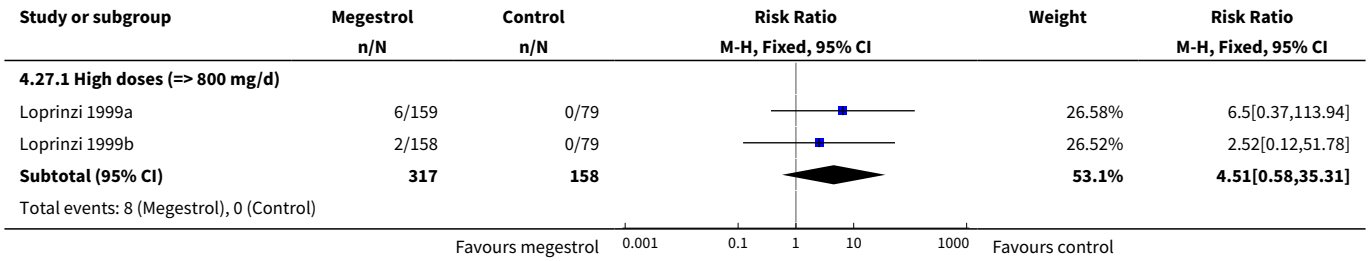
Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.25.1 High doses (=> 800 mg/d)					
Loprinzi 1999a	9/79	25/159		36.65%	0.72[0.36,1.48]
Loprinzi 1999b	8/79	13/158		19.14%	1.23[0.53,2.85]
Oster 1994	9/52	7/48		16.08%	1.19[0.48,2.94]
Von Roenn 1994	11/75	4/19		14.1%	0.7[0.25,1.95]
Subtotal (95% CI)	**285**	**384**		**85.97%**	**0.92[0.6,1.4]**
Total events: 37 (Megestrol), 49 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.48, df=3(P=0.69); I^2=0%					
Test for overall effect: Z=0.39(P=0.7)					
4.25.2 Low doses (< 800 mg/d)					

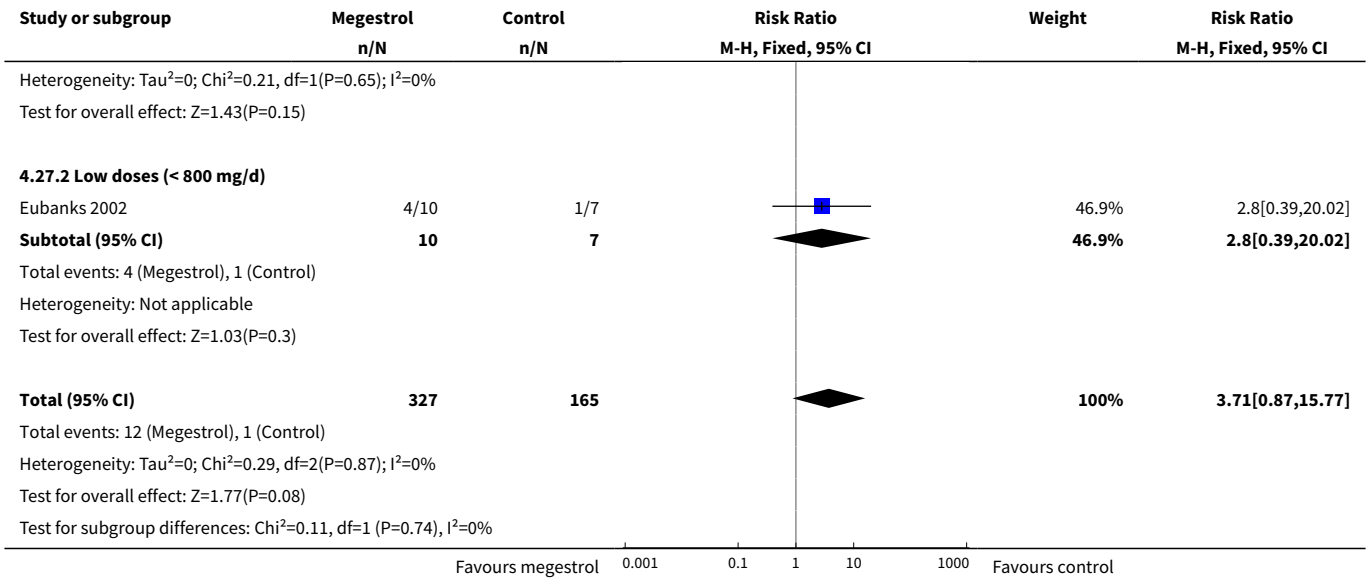


Analysis 4.26. Comparison 4 Safety, Outcome 26 Inappropriate behaviour.

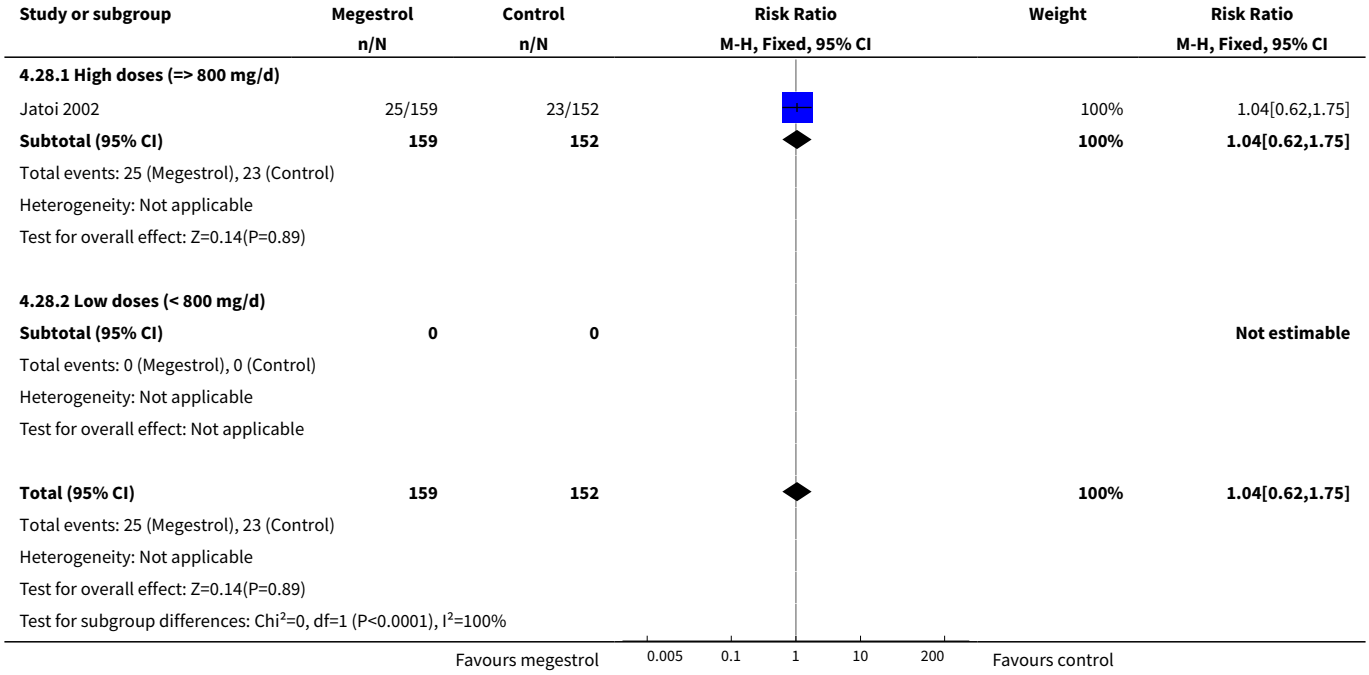


Analysis 4.27. Comparison 4 Safety, Outcome 27 Insomnia.

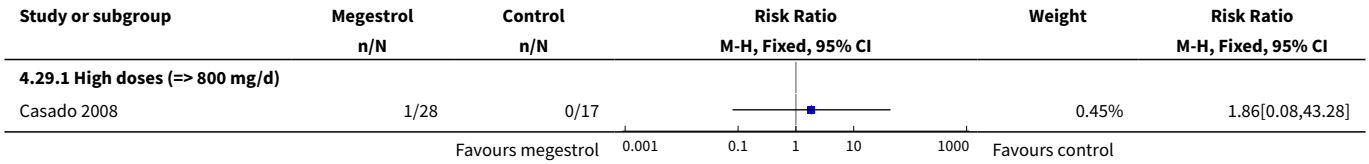


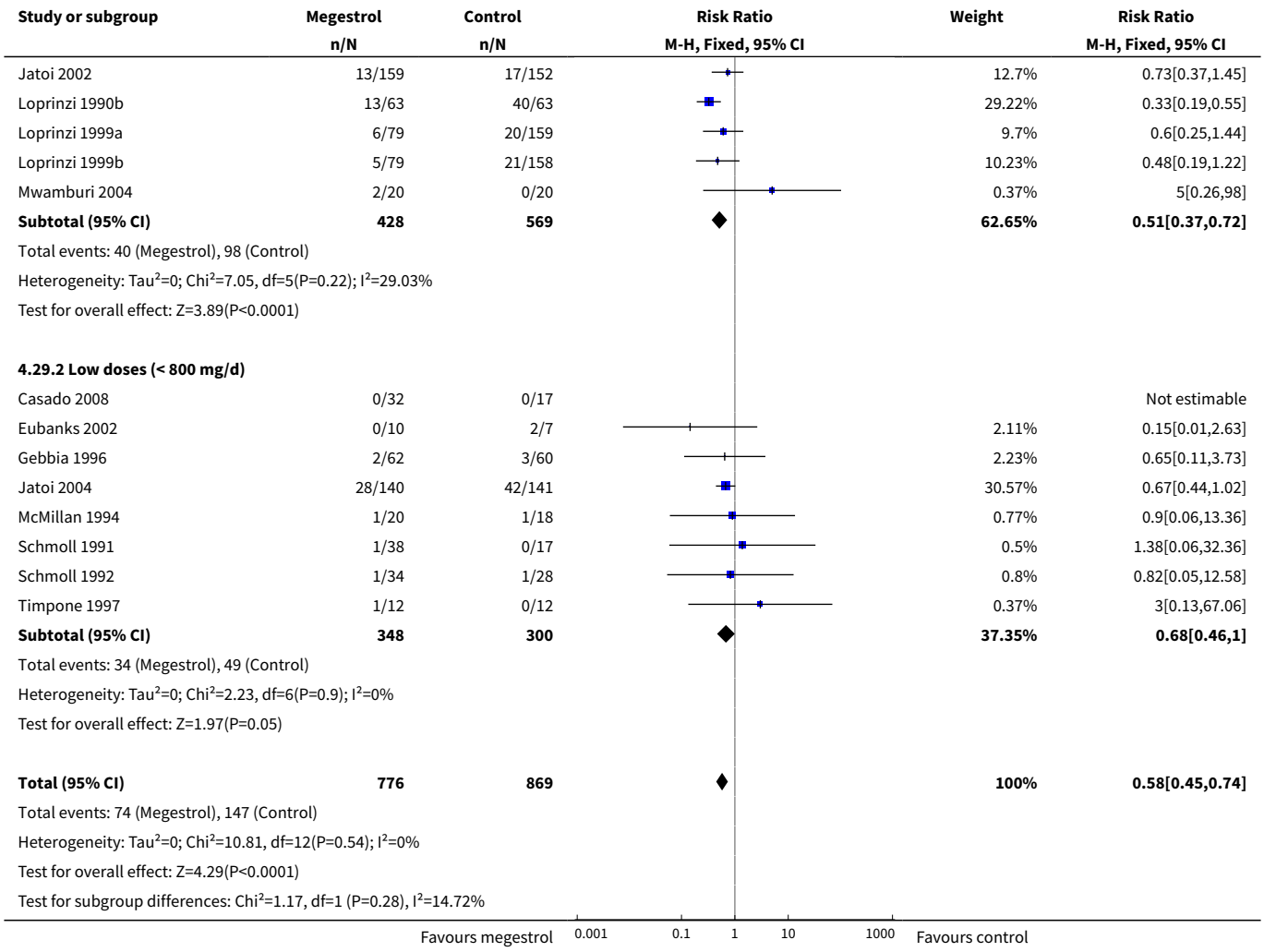


Analysis 4.28. Comparison 4 Safety, Outcome 28 Loss of co-ordination.

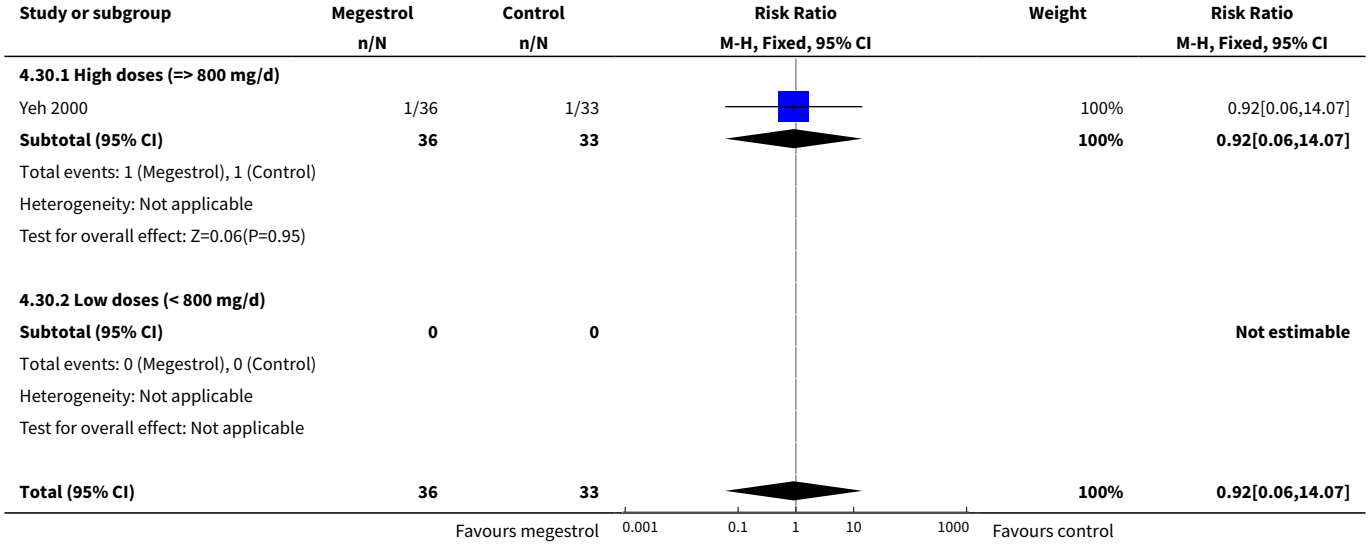


Analysis 4.29. Comparison 4 Safety, Outcome 29 Nausea/vomiting.

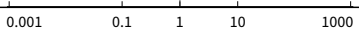




Analysis 4.30. Comparison 4 Safety, Outcome 30 Neoplasma.



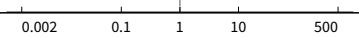
Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 1 (Megestrol), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					
Test for subgroup differences: Not applicable					



Favours megestrol Favours control

Analysis 4.31. Comparison 4 Safety, Outcome 31 Oedema.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.31.1 High doses (=> 800 mg/d)					
Casado 2008	12/28	7/17		8.82%	1.04[0.51,2.12]
Jatoi 2002	29/159	17/152		17.61%	1.63[0.94,2.84]
Loprinzi 1990b	18/63	8/63		8.1%	2.25[1.06,4.79]
Loprinzi 1999a	10/79	24/159		16.14%	0.84[0.42,1.67]
Loprinzi 1999b	9/79	13/158		8.78%	1.38[0.62,3.1]
Tchekmedyian 1992	8/49	6/40		6.69%	1.09[0.41,2.88]
Von Roenn 1994	1/75	2/19		3.23%	0.13[0.01,1.32]
Weisberg 2002	11/72	4/73		4.02%	2.79[0.93,8.35]
Subtotal (95% CI)	**604**	**681**		**73.41%**	**1.37[1.04,1.81]**
Total events: 98 (Megestrol), 81 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.35, df=7(P=0.17); I^2=32.38%					
Test for overall effect: Z=2.25(P=0.02)					
4.31.2 Low doses (< 800 mg/d)					
Beller 1997	4/161	0/79		0.68%	4.44[0.24,81.54]
Casado 2008	14/32	7/17		9.26%	1.06[0.53,2.12]
Feliu 1992	7/76	3/74		3.08%	2.27[0.61,8.45]
Gebbia 1996	11/62	9/60		9.27%	1.18[0.53,2.65]
Vadell 1998	2/99	0/51		0.67%	2.6[0.13,53.16]
Von Roenn 1994	13/167	2/19		3.64%	0.74[0.18,3.03]
Subtotal (95% CI)	**597**	**300**		**26.59%**	**1.33[0.84,2.09]**
Total events: 51 (Megestrol), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.63, df=5(P=0.76); I^2=0%					
Test for overall effect: Z=1.21(P=0.23)					
Total (95% CI)	**1201**	**981**		**100%**	**1.36[1.07,1.72]**
Total events: 149 (Megestrol), 102 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.06, df=13(P=0.44); I^2=0.45%					
Test for overall effect: Z=2.55(P=0.01)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%					



Favours megestrol Favours control

Analysis 4.32. Comparison 4 Safety, Outcome 32 Pneumonia.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.32.1 High doses (=> 800 mg/d)					
Weisberg 2002	2/72	0/73		13.86%	5.07[0.25,103.77]
Yeh 2000	1/36	2/33		58.24%	0.46[0.04,4.82]
Subtotal (95% CI)	**108**	**106**		**72.09%**	**1.34[0.28,6.54]**
Total events: 3 (Megestrol), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.55, df=1(P=0.21); I^2=35.29%					
Test for overall effect: Z=0.37(P=0.71)					
4.32.2 Low doses (< 800 mg/d)					
De Conno 1998	1/21	0/21		13.95%	3[0.13,69.7]
Herrejon 2011	1/20	0/20		13.95%	3[0.13,69.52]
Subtotal (95% CI)	**41**	**41**		**27.91%**	**3[0.32,27.71]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
Total (95% CI)	**149**	**147**		**100%**	**1.81[0.51,6.42]**
Total events: 5 (Megestrol), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.95, df=3(P=0.58); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					
Test for subgroup differences: Chi^2=0.33, df=1 (P=0.56), I^2=0%					

Analysis 4.33. Comparison 4 Safety, Outcome 33 Pruritus.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.33.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.33.2 Low doses (< 800 mg/d)					
Feliu 1992	1/76	0/74		24.95%	2.92[0.12,70.6]
Gebbia 1996	0/62	1/60		75.05%	0.32[0.01,7.77]
Subtotal (95% CI)	**138**	**134**		**100%**	**0.97[0.14,6.81]**
Total events: 1 (Megestrol), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=0.03(P=0.98)					
Total (95% CI)	**138**	**134**		**100%**	**0.97[0.14,6.81]**
Total events: 1 (Megestrol), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=0.03(P=0.98)					
Test for subgroup differences: Not applicable					

Analysis 4.34. Comparison 4 Safety, Outcome 34 Pyrosis.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.34.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.34.2 Low doses (< 800 mg/d)					
Feliu 1992	5/76	3/74		100%	1.62[0.4,6.55]
Subtotal (95% CI)	**76**	**74**		**100%**	**1.62[0.4,6.55]**
Total events: 5 (Megestrol), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.68(P=0.5)					
Total (95% CI)	**76**	**74**		**100%**	**1.62[0.4,6.55]**
Total events: 5 (Megestrol), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.68(P=0.5)					
Test for subgroup differences: Not applicable					

Analysis 4.35. Comparison 4 Safety, Outcome 35 Pulmonary embolism.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.35.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.35.2 Low doses (< 800 mg/d)					
Beller 1997	2/161	0/79		100%	2.47[0.12,50.83]
Subtotal (95% CI)	**161**	**79**		**100%**	**2.47[0.12,50.83]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
Total (95% CI)	**161**	**79**		**100%**	**2.47[0.12,50.83]**
Total events: 2 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
Test for subgroup differences: Not applicable					

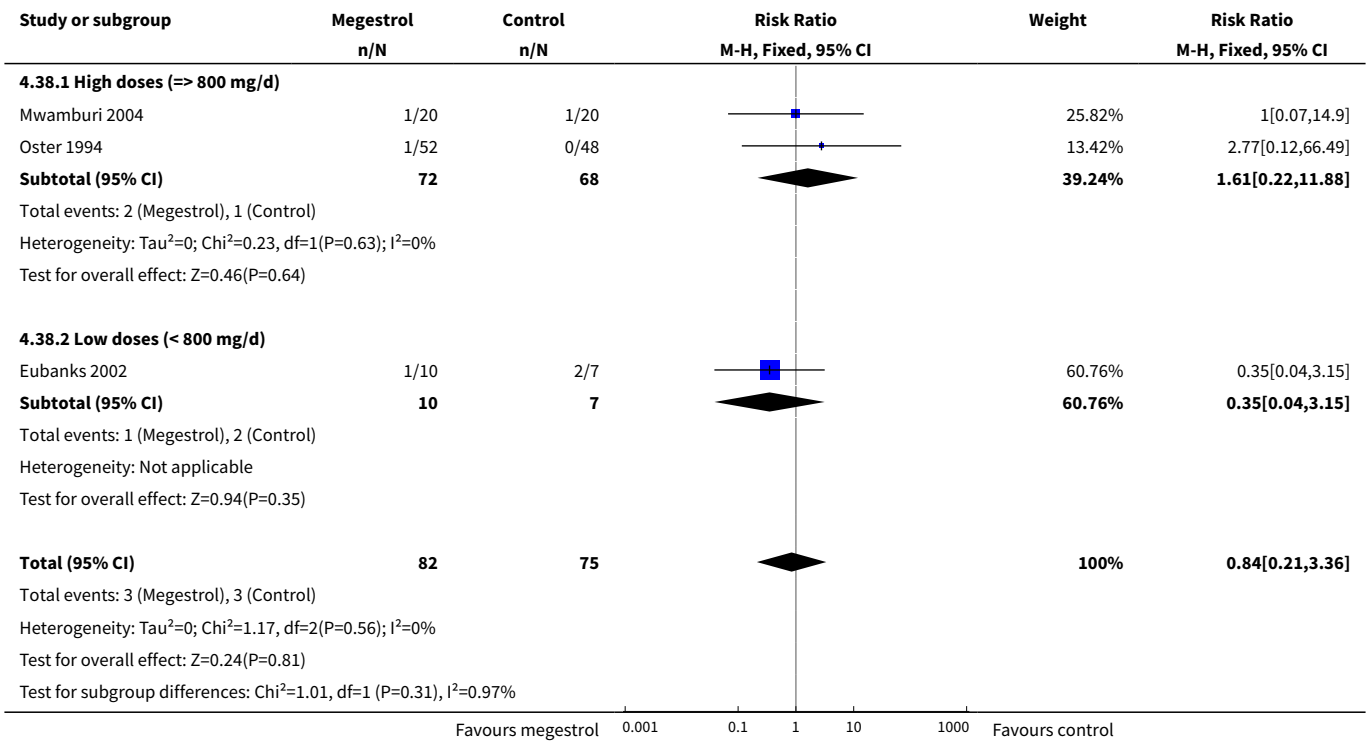
Analysis 4.36. Comparison 4 Safety, Outcome 36 Respiratory failure.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.36.1 High doses (=> 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.36.2 Low doses (< 800 mg/d)					
De Conno 1998	0/21	1/21		100%	0.33[0.01,7.74]
Subtotal (95% CI)	**21**	**21**		**100%**	**0.33[0.01,7.74]**
Total events: 0 (Megestrol), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.49)					
Total (95% CI)	**21**	**21**		**100%**	**0.33[0.01,7.74]**
Total events: 0 (Megestrol), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.49)					
Test for subgroup differences: Not applicable					

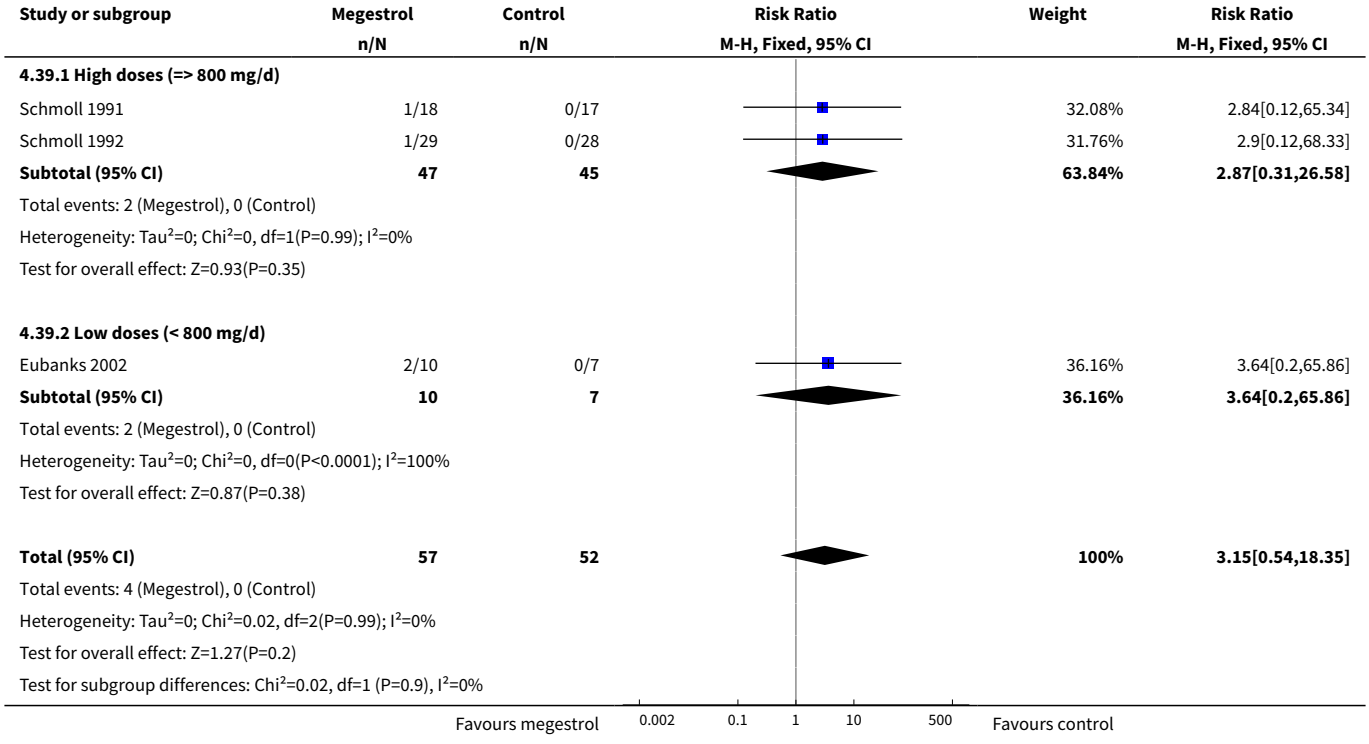
Analysis 4.37. Comparison 4 Safety, Outcome 37 Other adverse events.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.37.1 High doses (=> 800 mg/d)					
Mwamburi 2004	3/20	0/20		7.04%	7[0.38,127.32]
Weisberg 2002	0/72	3/73		48.91%	0.14[0.01,2.75]
Yeh 2000	7/36	3/33		44.05%	2.14[0.6,7.6]
Subtotal (95% CI)	**128**	**126**		**100%**	**1.51[0.6,3.76]**
Total events: 10 (Megestrol), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.8, df=2(P=0.15); I^2=47.38%					
Test for overall effect: Z=0.88(P=0.38)					
4.37.2 Low doses (< 800 mg/d)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**128**	**126**		**100%**	**1.51[0.6,3.76]**
Total events: 10 (Megestrol), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.8, df=2(P=0.15); I^2=47.38%					
Test for overall effect: Z=0.88(P=0.38)					
Test for subgroup differences: Not applicable					

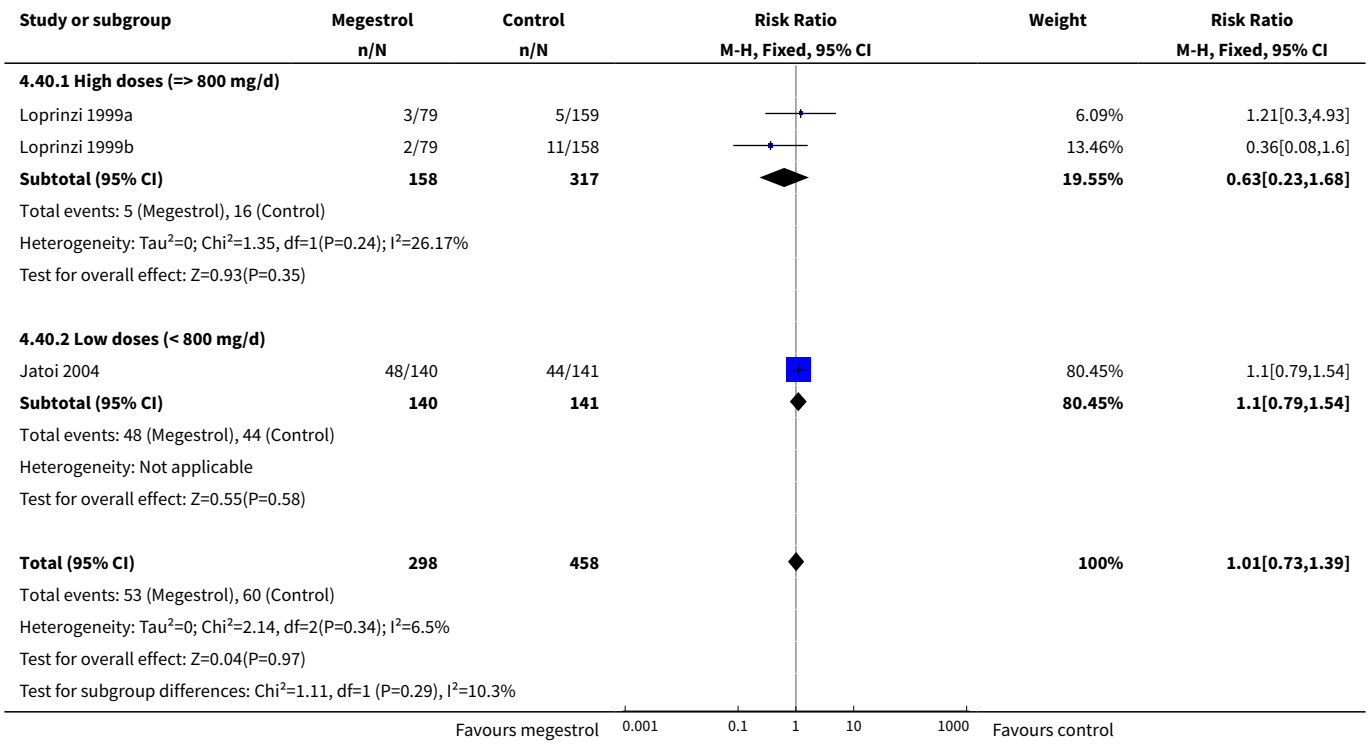
Analysis 4.38. Comparison 4 Safety, Outcome 38 Skin disorder (includes vesiculobullous rash).



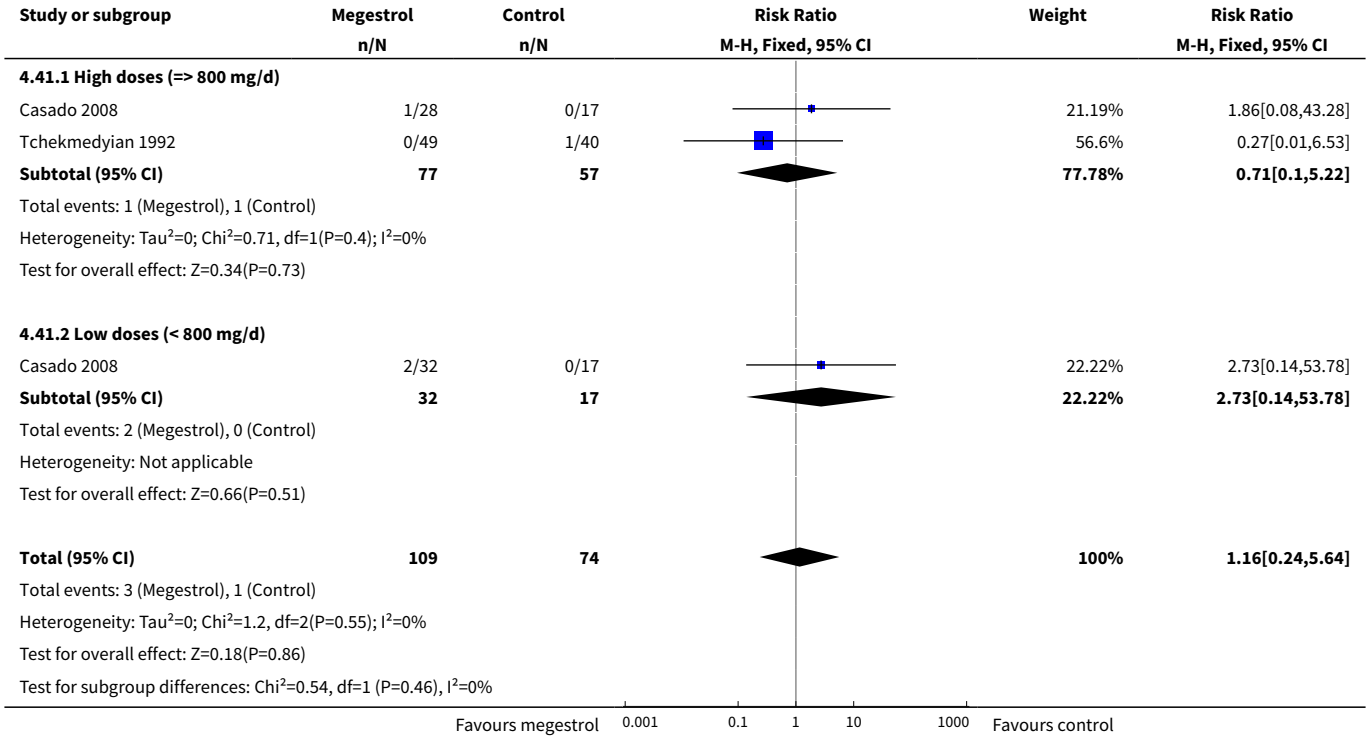
Analysis 4.39. Comparison 4 Safety, Outcome 39 Sweating.



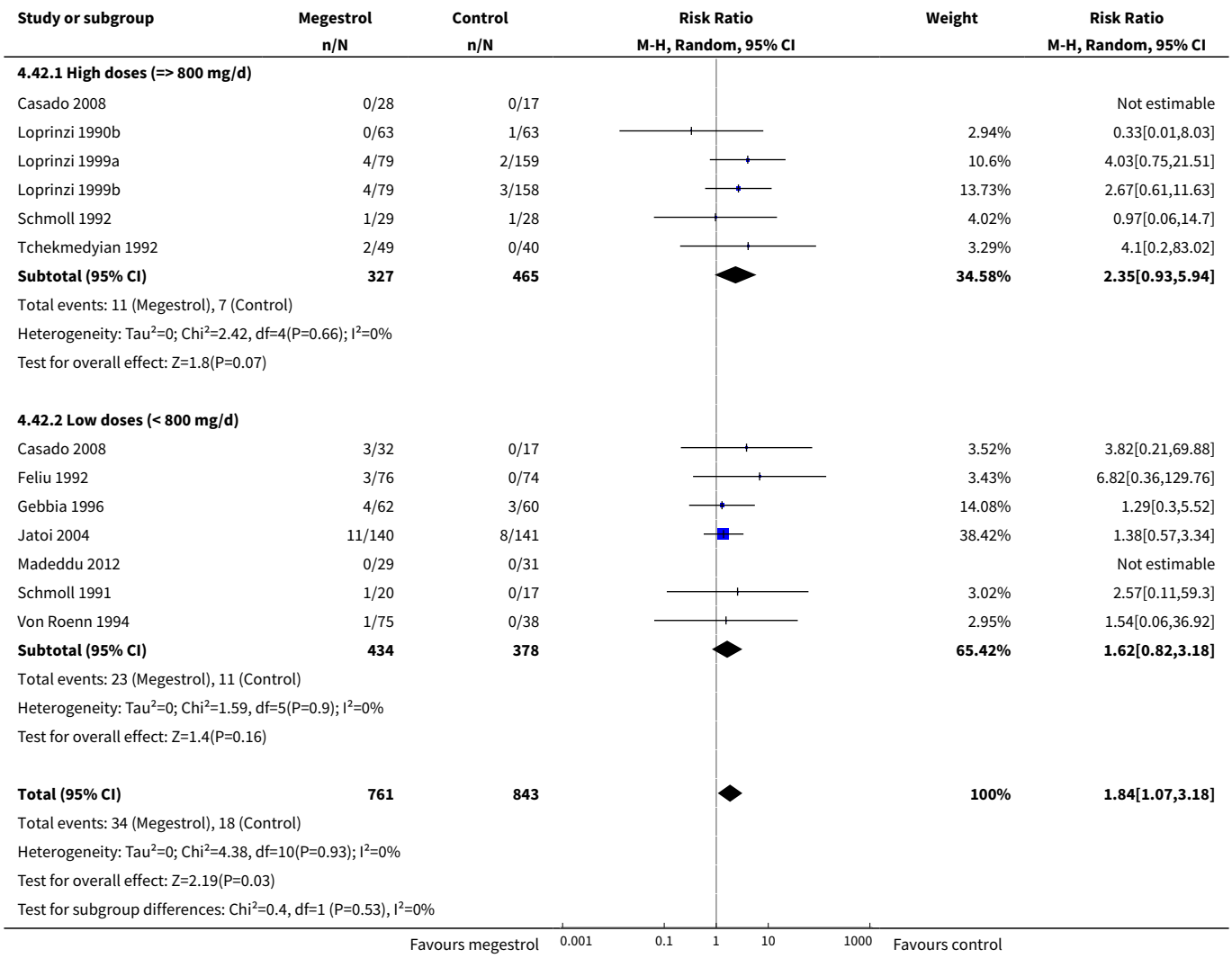
Analysis 4.40. Comparison 4 Safety, Outcome 40 Swelling legs or abdominal.



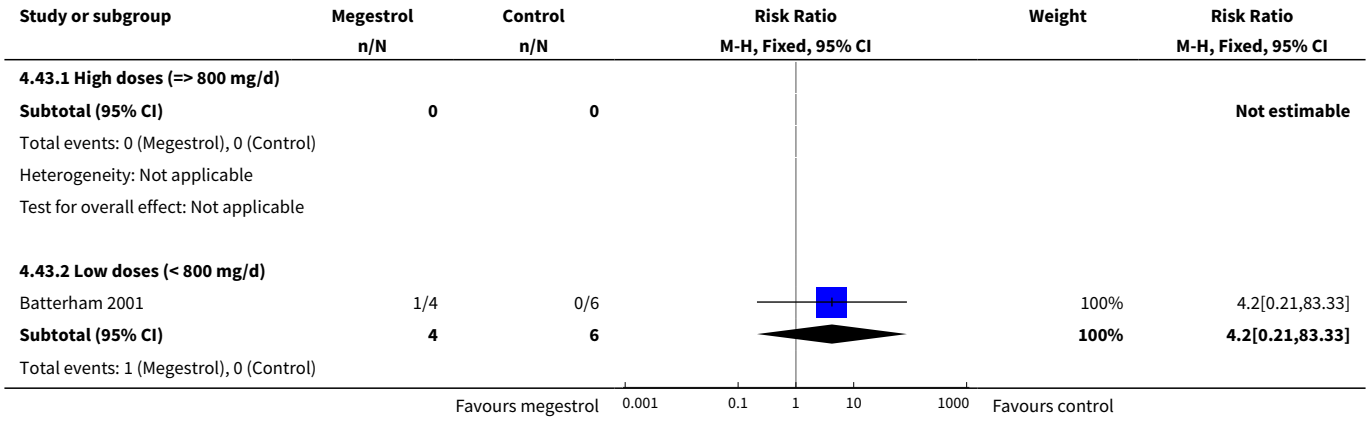
Analysis 4.41. Comparison 4 Safety, Outcome 41 Stroke.



Analysis 4.42. Comparison 4 Safety, Outcome 42 Thromboembolic phenomena including thrombophlebitis.



Analysis 4.43. Comparison 4 Safety, Outcome 43 Testicular shrinkage.



Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
Total (95% CI)	**4**	**6**		**100%**	**4.2[0.21,83.33]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
Test for subgroup differences: Not applicable					

Analysis 4.44. Comparison 4 Safety, Outcome 44 Withdrawals.

Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.44.1 High doses (=> 800 mg/d)					
Jatoi 2002	107/159	111/152		47.79%	0.92[0.8,1.07]
Loprinzi 1990b	9/67	9/66		3.82%	0.99[0.42,2.33]
Mwamburi 2004	2/20	5/20		2.11%	0.4[0.09,1.83]
Oster 1994	27/52	22/48		9.63%	1.13[0.76,1.7]
Tchekmedyian 1992	12/49	10/40		4.64%	0.98[0.47,2.03]
Weisberg 2002	6/72	11/73		4.6%	0.55[0.22,1.42]
Subtotal (95% CI)	**419**	**399**		**72.58%**	**0.92[0.8,1.06]**
Total events: 163 (Megestrol), 168 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.37, df=5(P=0.64); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					
4.44.2 Low doses (< 800 mg/d)					
De Conno 1998	4/21	5/21		2.11%	0.8[0.25,2.57]
Eubanks 2002	0/10	3/7		1.71%	0.1[0.01,1.74]
Fietkau 1996	1/32	2/32		0.84%	0.5[0.05,5.24]
Gebbia 1996	1/62	2/60		0.86%	0.48[0.05,5.2]
Giacosa 1997	5/15	5/15		2.11%	1[0.36,2.75]
Herrejon 2011	5/20	5/20		2.11%	1[0.34,2.93]
Macbeth 1994	28/38	20/37		8.53%	1.36[0.96,1.94]
McMillan 1994	9/20	8/18		3.55%	1.01[0.5,2.06]
Timpone 1997	2/12	5/12		2.11%	0.4[0.1,1.67]
Yeh 2000	10/36	8/33		3.51%	1.15[0.51,2.55]
Subtotal (95% CI)	**266**	**255**		**27.42%**	**0.98[0.75,1.28]**
Total events: 65 (Megestrol), 63 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.16, df=9(P=0.52); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					
Total (95% CI)	**685**	**654**		**100%**	**0.94[0.83,1.06]**
Total events: 228 (Megestrol), 231 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.35, df=15(P=0.65); I^2=0%					
Test for overall effect: Z=1.02(P=0.31)					
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.65), I^2=0%					

Comparison 5. Sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Appetite improvement treatment duration 6 weeks	7	1174	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.14, 2.54]
1.1 < 6 weeks	1	133	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.87, 2.52]
1.2 6 or more weeks	6	1041	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.11, 2.86]
2 Appetite improvement treatment duration 12 weeks	7	1174	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.14, 2.54]
2.1 0 to 11 weeks	6	904	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.06, 3.04]
2.2 12 or more weeks	1	270	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.13, 2.16]
3 Appetite gain 12 weeks	3	84	Mean Difference (IV, Random, 95% CI)	1.45 [0.35, 2.54]
3.1 < 12 weeks	1	27	Mean Difference (IV, Random, 95% CI)	2.53 [0.89, 4.17]
3.2 > 12 weeks	2	57	Mean Difference (IV, Random, 95% CI)	0.94 [0.32, 1.56]
4 Weight improvement treatment duration 6 weeks	17	2237	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.21, 1.98]
4.1 < 6 weeks	1	133	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.40]
4.2 6 or more weeks	16	2104	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.27, 2.10]
5 Quality of life gain	3	381	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-0.02, 0.65]
5.1 Cancer	2	344	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.01, 0.41]
5.2 Other underlying pathology	1	37	Std. Mean Difference (IV, Random, 95% CI)	0.82 [0.14, 1.50]
6 Weight improvement 12 weeks	17	2237	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.01, 1.94]
6.1 < 12 weeks	12	1744	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.90, 2.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 > 12 weeks	5	493	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.92, 2.31]
7 Weight gain 6 weeks	13	1093	Mean Difference (IV, Random, 95% CI)	1.96 [1.11, 2.81]
7.1 < 6 weeks	2	166	Mean Difference (IV, Random, 95% CI)	1.46 [0.62, 2.30]
7.2 6 or more weeks	11	927	Mean Difference (IV, Random, 95% CI)	2.15 [1.09, 3.21]
8 Weight gain 12 weeks	13	1093	Mean Difference (IV, Random, 95% CI)	1.96 [1.11, 2.81]
8.1 < 12 weeks	11	1025	Mean Difference (IV, Random, 95% CI)	1.96 [1.06, 2.87]
8.2 > 12 weeks	2	68	Mean Difference (IV, Random, 95% CI)	1.94 [-1.64, 5.53]
9 Blinded versus open-label appetite improvement	7	1174	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.14, 2.54]
9.1 Blinded studies	3	553	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.17, 3.27]
9.2 Open-label studies	4	621	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.82, 2.87]
10 Blinded versus open-label appetite gain	3	84	Mean Difference (IV, Random, 95% CI)	1.45 [0.35, 2.54]
10.1 Blinded studies	2	75	Mean Difference (IV, Random, 95% CI)	1.54 [-0.01, 3.08]
10.2 Open-label studies	1	9	Mean Difference (IV, Random, 95% CI)	1.60 [-1.28, 4.48]
11 Blinded versus open-label weight Improvement	17	2237	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.01, 1.94]
11.1 Blinded studies	10	1552	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.15, 2.32]
11.2 Open-label studies	7	685	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.53, 2.47]
12 Sensitivity number patients weight improvement	17	2237	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.01, 1.94]
12.1 n < 100 patients	9	467	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.98, 1.65]

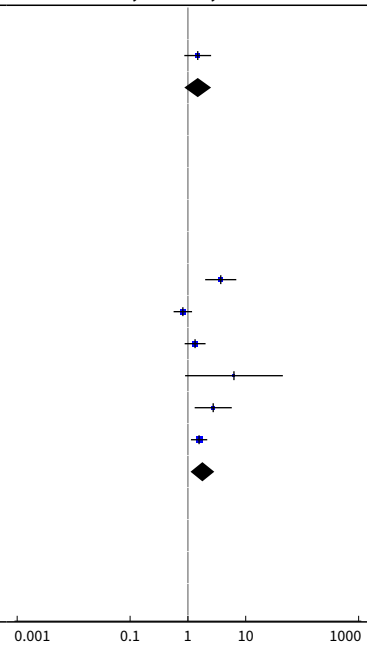
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.2 n > 100 patients	8	1770	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.80, 2.91]
13 Appetite improvement, study quality	7	1174	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.14, 2.54]
13.1 Study quality (Jadad score 3, 4 or 5)	2	283	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.93, 5.72]
13.2 Study quality (Jadad score 2 or low)	5	891	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.96, 2.27]
14 Weight improvement, study quality	17	2237	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.21, 1.98]
14.1 Study quality (Jadad score 3,4 or 5)	10	1322	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.07, 2.10]
14.2 Study quality (Jadad score 2 or low)	7	915	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.17, 2.20]
15 Weight gain, study quality	13	1093	Mean Difference (IV, Random, 95% CI)	1.96 [1.11, 2.81]
15.1 Study quality (Jadad score 3,4 or 5)	9	528	Mean Difference (IV, Random, 95% CI)	1.90 [0.89, 2.91]
15.2 Study quality (Jadad score 0 or low)	4	565	Mean Difference (IV, Random, 95% CI)	2.30 [0.25, 4.35]
16 Sensitivity duration oedema	13	2236	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.12, 1.72]
16.1 1 to 4 weeks	4	638	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.07, 3.08]
16.2 > 5 to 8 weeks	7	1225	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.04, 1.97]
16.3 9 to 12 weeks	2	373	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.82, 1.46]
16.4 > 12 weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Sensitivity duration thromboembolic phenomena	12	1604	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.11, 3.17]
17.1 < 12 weeks	7	934	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.16, 5.76]
17.2 > 12 weeks	5	670	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.71, 2.94]
18 Sensitivity blinded versus open-label weight gain	14	1214	Mean Difference (IV, Random, 95% CI)	2.42 [1.41, 3.43]
18.1 Blinded studies	9	673	Mean Difference (IV, Random, 95% CI)	1.69 [1.11, 2.28]

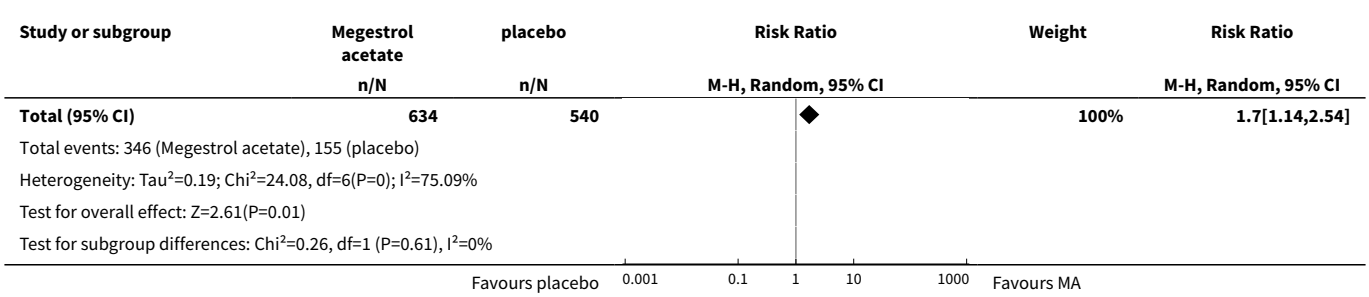
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
18.2 Open-label studies	5	541	Mean Difference (IV, Random, 95% CI)	3.15 [-0.89, 7.19]
19 Sensitivity number of patients in trial appetite improvement	7	1174	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.14, 2.54]
19.1 n < 100 patients	2	146	Risk Ratio (M-H, Random, 95% CI)	3.04 [1.52, 6.07]
19.2 n > 100 patients	5	1028	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.99, 2.27]
20 Sensitivity number of patients weight gain	14	1214	Mean Difference (IV, Random, 95% CI)	2.42 [1.41, 3.43]
20.1 n < 100 patients	8	252	Mean Difference (IV, Random, 95% CI)	3.45 [0.82, 6.08]
20.2 n > 100 patients	6	962	Mean Difference (IV, Random, 95% CI)	1.13 [0.59, 1.68]
21 Sensitivity appetite improvement cancer	6	904	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.06, 3.04]
21.1 Cancer	6	904	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.06, 3.04]
22 Appetite improvement doses	7	1174	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.14, 2.54]
22.1 ≤ 400 mg of MA/d	3	553	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.17, 3.27]
22.2 480 to 800 mg of MA/d	2	146	Risk Ratio (M-H, Random, 95% CI)	3.04 [1.52, 6.07]
22.3 ≥ 800 mg of MA/d	2	475	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.67]
23 Weight improvement doses	17	2237	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.21, 1.97]
23.1 ≤ 400 mg MA/d	7	818	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.19, 2.60]
23.2 480 to 800 mg MA/d	10	1330	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.00, 2.12]
23.3 ≥ 800 mg MA/d	1	89	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.87, 2.17]
24 Sensitivity (cancer/other patients) thromboembolic phenomena	12	1604	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.11, 3.17]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
24.1 Cancer patients	11	1491	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.11, 3.22]
24.2 Other patients	1	113	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.06, 36.92]
25 Deaths sensitivity 6 weeks	11	1367	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.01, 1.89]
25.1 < 6 weeks	3	205	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.56, 2.86]
25.2 > 6 weeks	8	1162	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.00, 1.97]
26 Deaths sensitivity/pathology	11	1367	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.01, 1.89]
26.1 Cancer	7	801	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.97, 1.85]
26.2 AIDS	3	497	Risk Ratio (M-H, Random, 95% CI)	2.55 [0.63, 10.28]
26.3 Other underlying pathology	1	69	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.06, 14.07]

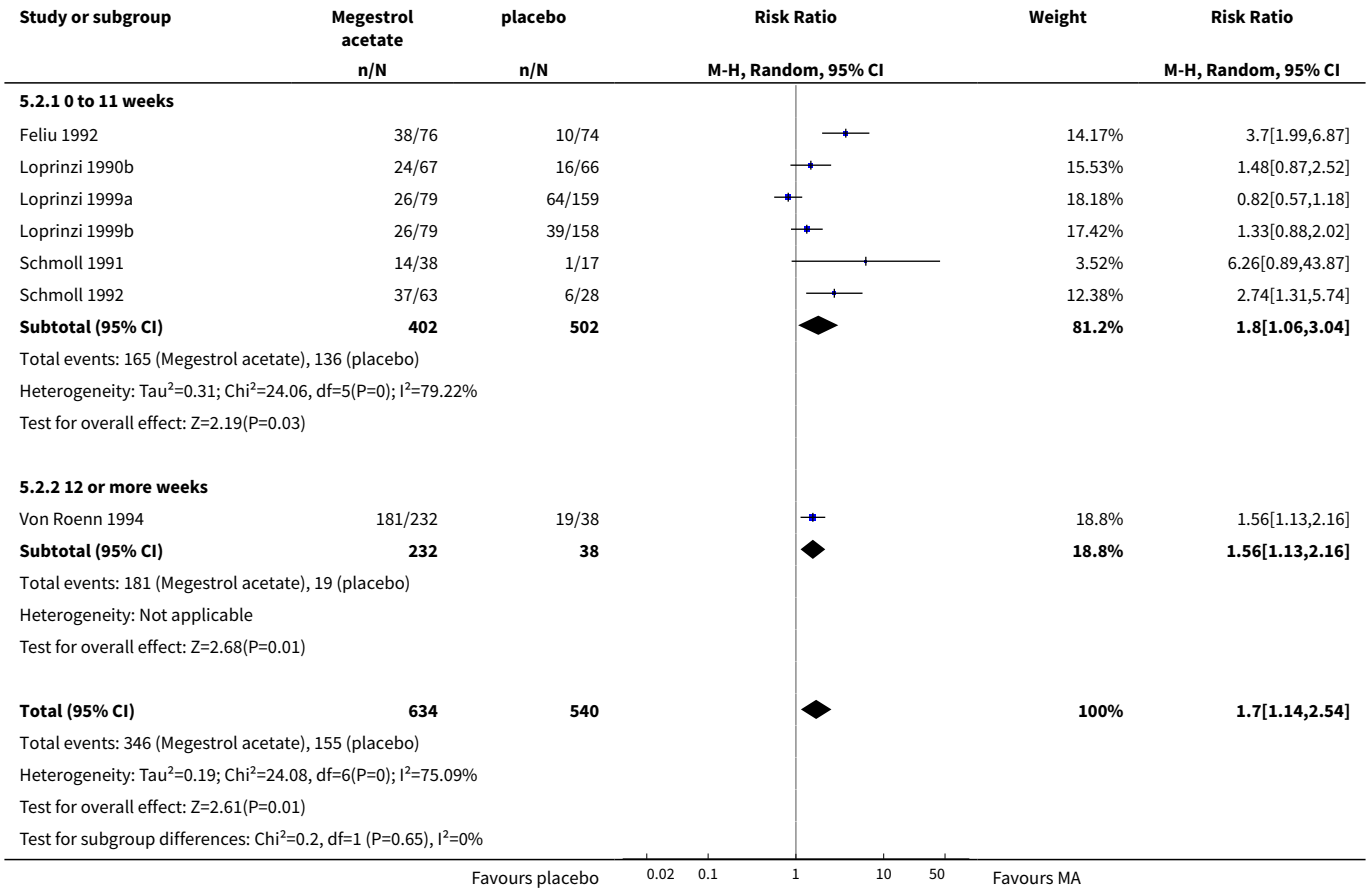
Analysis 5.1. Comparison 5 Sensitivity analyses, Outcome 1 Appetite improvement treatment duration 6 weeks.

Study or subgroup	Megestrol acetate n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 < 6 weeks					
Loprinzi 1990b	24/67	16/66		15.53%	1.48[0.87,2.52]
Subtotal (95% CI)	**67**	**66**		**15.53%**	**1.48[0.87,2.52]**
Total events: 24 (Megestrol acetate), 16 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					
5.1.2 6 or more weeks					
Feliu 1992	38/76	10/74		14.17%	3.7[1.99,6.87]
Loprinzi 1999a	26/79	64/159		18.18%	0.82[0.57,1.18]
Loprinzi 1999b	26/79	39/158		17.42%	1.33[0.88,2.02]
Schmoll 1991	14/38	1/17		3.52%	6.26[0.89,43.87]
Schmoll 1992	37/63	6/28		12.38%	2.74[1.31,5.74]
Von Roenn 1994	181/232	19/38		18.8%	1.56[1.13,2.16]
Subtotal (95% CI)	**567**	**474**		**84.47%**	**1.78[1.11,2.86]**
Total events: 322 (Megestrol acetate), 139 (placebo)					
Heterogeneity: Tau^2=0.24; Chi^2=24.15, df=5(P=0); I^2=79.3%					
Test for overall effect: Z=2.38(P=0.02)					

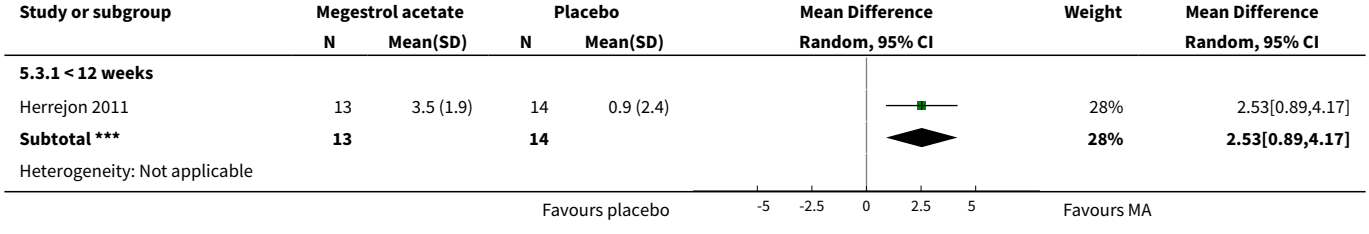




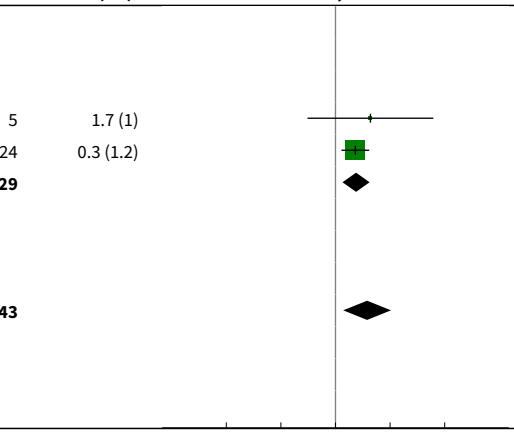
Analysis 5.2. Comparison 5 Sensitivity analyses, Outcome 2 Appetite improvement treatment duration 12 weeks.



Analysis 5.3. Comparison 5 Sensitivity analyses, Outcome 3 Appetite gain 12 weeks.

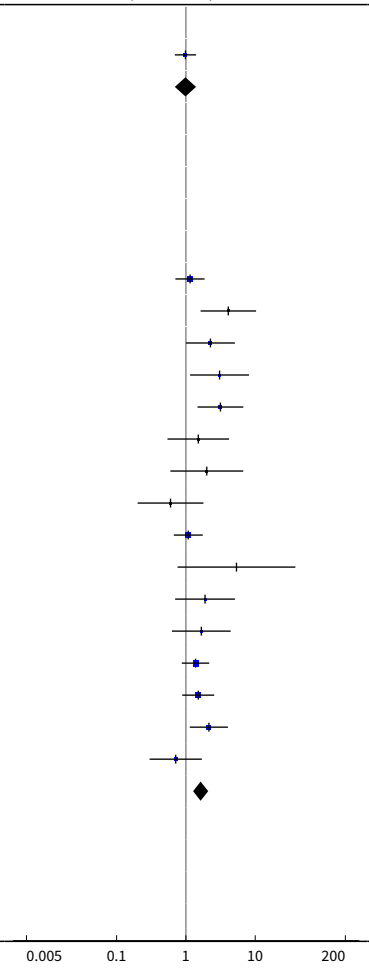


Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=3.03(P=0)							
5.3.2 > 12 weeks							
Batterham 2001	4	3.3 (2.8)	5	1.7 (1)		12.12%	1.6[-1.28,4.48]
Yeh 2000	24	1.2 (1)	24	0.3 (1.2)		59.88%	0.91[0.27,1.55]
Subtotal ***	**28**		**29**			**72%**	**0.94[0.32,1.56]**
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%							
Test for overall effect: Z=2.97(P=0)							
Total ***	**41**		**43**			**100%**	**1.45[0.35,2.54]**
Heterogeneity: Tau^2=0.42; Chi^2=3.36, df=2(P=0.19); I^2=40.52%							
Test for overall effect: Z=2.59(P=0.01)							
Test for subgroup differences: Chi^2=3.15, df=1 (P=0.08), I^2=68.27%							



Analysis 5.4. Comparison 5 Sensitivity analyses, Outcome 4 Weight improvement treatment duration 6 weeks.

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.4.1 < 6 weeks					
Loprinzi 1990b	32/67	32/66		10.78%	0.99[0.69,1.4]
Subtotal (95% CI)	**67**	**66**		**10.78%**	**0.99[0.69,1.4]**
Total events: 32 (Megestrol acetate), 32 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.93)					
5.4.2 6 or more weeks					
Batterham 2001	4/4	5/6		8.99%	1.15[0.71,1.86]
Feliu 1992	21/76	5/74		4.67%	4.09[1.63,10.27]
Fietkau 1996	14/31	6/30		5.47%	2.26[1,5.1]
Jatoi 2002	16/159	5/152		4.3%	3.06[1.15,8.14]
Jatoi 2004	25/140	8/141		5.92%	3.15[1.47,6.74]
Loprinzi 1999a	6/79	8/159		4.04%	1.51[0.54,4.2]
Loprinzi 1999b	5/79	5/158		3.15%	2[0.6,6.71]
McMillan 1994	4/20	6/18		3.68%	0.6[0.2,1.79]
Mwamburi 2004	13/20	12/20		9.04%	1.08[0.67,1.75]
Schmoll 1991	12/38	1/17		1.4%	5.37[0.76,38.04]
Schmoll 1992	17/63	4/28		4.21%	1.89[0.7,5.1]
Summerbell 1992	5/7	3/7		4.32%	1.67[0.63,4.42]
Tchekmedyian 1992	27/49	16/40		9.37%	1.38[0.87,2.17]
Vadell 1998	38/99	13/51		8.39%	1.51[0.89,2.56]
Von Roenn 1994	105/232	8/38		7.21%	2.15[1.14,4.04]
Yeh 2000	7/36	9/33		5.05%	0.71[0.3,1.7]
Subtotal (95% CI)	**1132**	**972**		**89.22%**	**1.63[1.27,2.1]**
Total events: 319 (Megestrol acetate), 114 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=25.63, df=15(P=0.04); I^2=41.48%					
Test for overall effect: Z=3.82(P=0)					



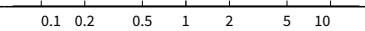
Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**1199**	**1038**		**100%**	**1.55[1.21,1.98]**
Total events: 351 (Megestrol acetate), 146 (Placebo)					
Heterogeneity: Tau²=0.11; Chi²=31.03, df=16(P=0.01); I²=48.43%					
Test for overall effect: Z=3.52(P=0)					
Test for subgroup differences: Chi²=5.22, df=1 (P=0.02), I²=80.84%					

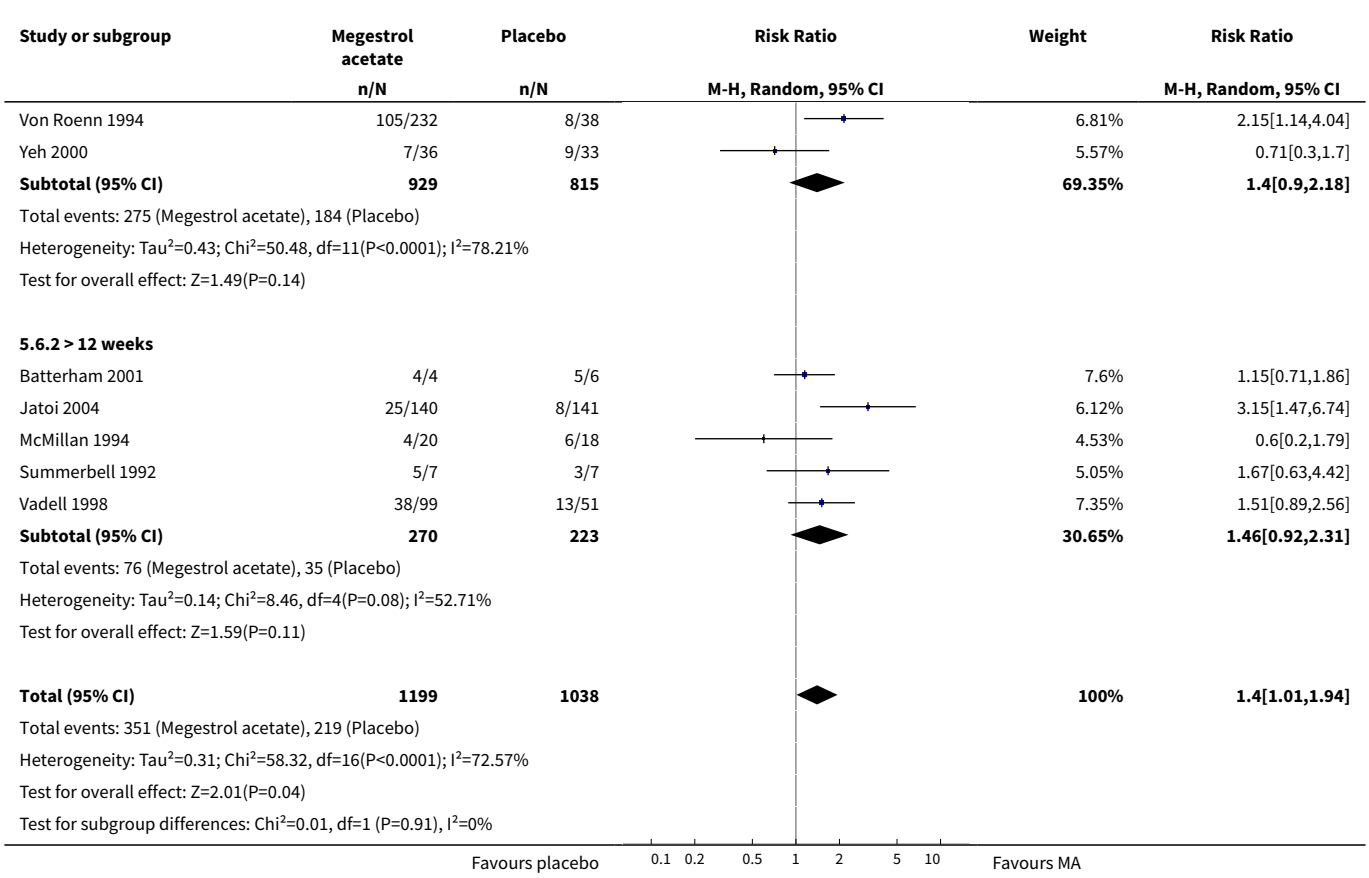
Analysis 5.5. Comparison 5 Sensitivity analyses, Outcome 5 Quality of life gain.

Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
5.5.1 Cancer							
De Conno 1998	17	-0.6 (8.3)	16	-1.9 (5.4)		18.47%	0.18[-0.51,0.86]
Jatoi 2002	159	15 (19)	152	12 (8)		62.71%	0.2[-0.02,0.43]
Subtotal ***	**176**		**168**			**81.18%**	**0.2[-0.01,0.41]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.95); I²=0%							
Test for overall effect: Z=1.86(P=0.06)							
5.5.2 Other underlying pathology							
Yeh 2000	17	7.8 (4.2)	20	4.7 (3.3)		18.82%	0.82[0.14,1.5]
Subtotal ***	**17**		**20**			**18.82%**	**0.82[0.14,1.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.38(P=0.02)							
Total ***	**193**		**188**			**100%**	**0.32[-0.02,0.65]**
Heterogeneity: Tau²=0.03; Chi²=2.94, df=2(P=0.23); I²=31.91%							
Test for overall effect: Z=1.87(P=0.06)							
Test for subgroup differences: Chi²=2.93, df=1 (P=0.09), I²=65.9%							

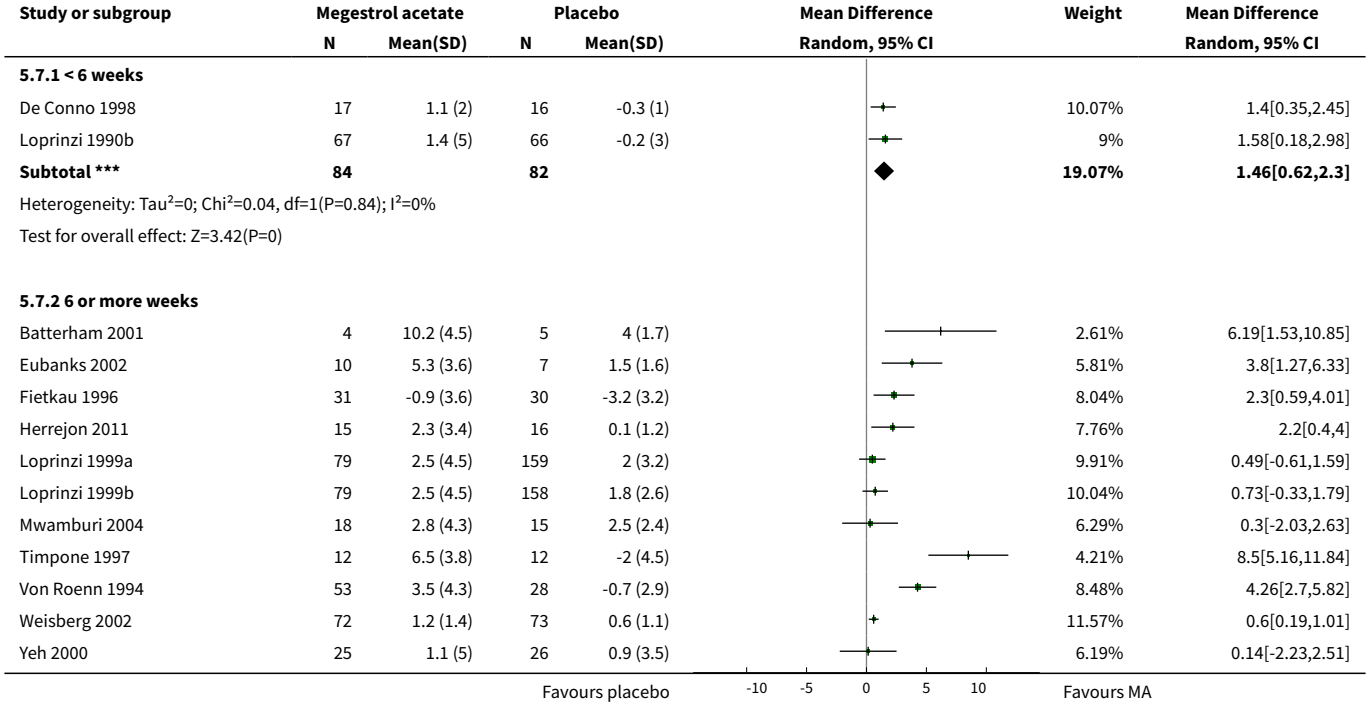
Analysis 5.6. Comparison 5 Sensitivity analyses, Outcome 6 Weight improvement 12 weeks.

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.6.1 < 12 weeks					
Feliu 1992	21/76	5/74		5.31%	4.09[1.63,10.27]
Fietkau 1996	14/31	6/30		5.84%	2.26[1,5.1]
Jatoi 2002	16/159	5/152		5.03%	3.06[1.15,8.14]
Loprinzi 1990b	32/67	32/66		8.24%	0.99[0.69,1.4]
Loprinzi 1999a	6/79	81/159		6%	0.15[0.07,0.33]
Loprinzi 1999b	5/79	5/158		4.07%	2[0.6,6.71]
Mwamburi 2004	13/20	12/20		7.62%	1.08[0.67,1.75]
Schmoll 1991	12/38	1/17		2.15%	5.37[0.76,38.04]
Schmoll 1992	17/63	4/28		4.97%	1.89[0.7,5.1]
Tchekmedyian 1992	27/49	16/40		7.75%	1.38[0.87,2.17]

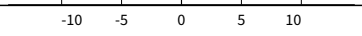




Analysis 5.7. Comparison 5 Sensitivity analyses, Outcome 7 Weight gain 6 weeks.

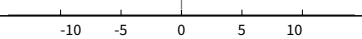


Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**398**		**529**			**80.93%**	**2.15[1.09,3.21]**
Heterogeneity: Tau²=2.18; Chi²=55.07, df=10(P<0.0001); I²=81.84%							
Test for overall effect: Z=3.98(P<0.0001)							
Total ***	**482**		**611**			**100%**	**1.96[1.11,2.81]**
Heterogeneity: Tau²=1.59; Chi²=56.05, df=12(P<0.0001); I²=78.59%							
Test for overall effect: Z=4.51(P<0.0001)							
Test for subgroup differences: Chi²=0.99, df=1 (P=0.32), I²=0%							



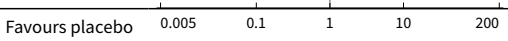
Analysis 5.8. Comparison 5 Sensitivity analyses, Outcome 8 Weight gain 12 weeks.

Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.8.1 < 12 weeks							
Batterham 2001	4	10.2 (4.5)	5	4 (1.7)		2.61%	6.19[1.53,10.85]
De Conno 1998	17	1.1 (2)	16	-0.3 (1)		10.07%	1.4[0.35,2.45]
Fietkau 1996	31	-0.9 (3.6)	30	-3.2 (3.2)		8.04%	2.3[0.59,4.01]
Herrejon 2011	15	2.3 (3.4)	16	0.1 (1.2)		7.76%	2.2[0.4,4]
Loprinzi 1990b	67	1.4 (5)	66	-0.2 (3)		9%	1.58[0.18,2.98]
Loprinzi 1999a	79	2.5 (4.5)	159	2 (3.2)		9.91%	0.49[-0.61,1.59]
Loprinzi 1999b	79	2.5 (4.5)	158	1.8 (2.6)		10.04%	0.73[-0.33,1.79]
Mwamburi 2004	18	2.8 (4.3)	15	2.5 (2.4)		6.29%	0.3[-2.03,2.63]
Timpone 1997	12	6.5 (3.8)	12	-2 (4.5)		4.21%	8.5[5.16,11.84]
Von Roenn 1994	53	3.5 (4.3)	28	-0.7 (2.9)		8.48%	4.26[2.7,5.82]
Weisberg 2002	72	1.2 (1.4)	73	0.6 (1.1)		11.57%	0.6[0.19,1.01]
Subtotal ***	**447**		**578**			**88%**	**1.96[1.06,2.87]**
Heterogeneity: Tau²=1.57; Chi²=50.97, df=10(P<0.0001); I²=80.38%							
Test for overall effect: Z=4.26(P<0.0001)							
5.8.2 > 12 weeks							
Eubanks 2002	10	5.3 (3.6)	7	1.5 (1.6)		5.81%	3.8[1.27,6.33]
Yeh 2000	25	1.1 (5)	26	0.9 (3.5)		6.19%	0.14[-2.23,2.51]
Subtotal ***	**35**		**33**			**12%**	**1.94[-1.64,5.53]**
Heterogeneity: Tau²=5.14; Chi²=4.29, df=1(P=0.04); I²=76.67%							
Test for overall effect: Z=1.06(P=0.29)							
Total ***	**482**		**611**			**100%**	**1.96[1.11,2.81]**
Heterogeneity: Tau²=1.59; Chi²=56.05, df=12(P<0.0001); I²=78.59%							
Test for overall effect: Z=4.51(P<0.0001)							
Test for subgroup differences: Chi²=0, df=1 (P=0.99), I²=0%							



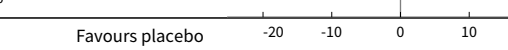
Analysis 5.9. Comparison 5 Sensitivity analyses, Outcome 9 Blinded versus open-label appetite improvement.

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.9.1 Blinded studies					
Feliu 1992	38/76	10/74		14.17%	3.7[1.99,6.87]
Loprinzi 1990b	24/67	16/66		15.53%	1.48[0.87,2.52]
Von Roenn 1994	181/232	19/38		18.8%	1.56[1.13,2.16]
Subtotal (95% CI)	**375**	**178**		**48.51%**	**1.96[1.17,3.27]**
Total events: 243 (Megestrol acetate), 45 (Placebo)					
Heterogeneity: Tau^2=0.14; Chi^2=6.74, df=2(P=0.03); I^2=70.34%					
Test for overall effect: Z=2.56(P=0.01)					
5.9.2 Open-label studies					
Loprinzi 1999a	26/79	64/159		18.18%	0.82[0.57,1.18]
Loprinzi 1999b	26/79	39/158		17.42%	1.33[0.88,2.02]
Schmoll 1991	14/38	1/17		3.52%	6.26[0.89,43.87]
Schmoll 1992	37/63	6/28		12.38%	2.74[1.31,5.74]
Subtotal (95% CI)	**259**	**362**		**51.49%**	**1.53[0.82,2.87]**
Total events: 103 (Megestrol acetate), 110 (Placebo)					
Heterogeneity: Tau^2=0.27; Chi^2=12.47, df=3(P=0.01); I^2=75.94%					
Test for overall effect: Z=1.34(P=0.18)					
Total (95% CI)	**634**	**540**		**100%**	**1.7[1.14,2.54]**
Total events: 346 (Megestrol acetate), 155 (Placebo)					
Heterogeneity: Tau^2=0.19; Chi^2=24.08, df=6(P=0); I^2=75.09%					
Test for overall effect: Z=2.61(P=0.01)					
Test for subgroup differences: Chi^2=0.35, df=1 (P=0.56), I^2=0%					



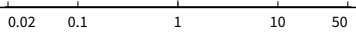
Analysis 5.10. Comparison 5 Sensitivity analyses, Outcome 10 Blinded versus open-label appetite gain.

Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.10.1 Blinded studies							
Herrejon 2011	13	3.5 (1.9)	14	0.9 (2.4)		28%	2.53[0.89,4.17]
Yeh 2000	24	1.2 (1)	24	0.3 (1.2)		59.88%	0.91[0.27,1.55]
Subtotal ***	**37**		**38**			**87.88%**	**1.54[-0.01,3.08]**
Heterogeneity: Tau^2=0.91; Chi^2=3.26, df=1(P=0.07); I^2=69.33%							
Test for overall effect: Z=1.95(P=0.05)							
5.10.2 Open-label studies							
Batterham 2001	4	3.3 (2.8)	5	1.7 (1)		12.12%	1.6[-1.28,4.48]
Subtotal ***	**4**		**5**			**12.12%**	**1.6[-1.28,4.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.09(P=0.28)							
Total ***	**41**		**43**			**100%**	**1.45[0.35,2.54]**
Heterogeneity: Tau^2=0.42; Chi^2=3.36, df=2(P=0.19); I^2=40.52%							
Test for overall effect: Z=2.59(P=0.01)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.97), I^2=0%							



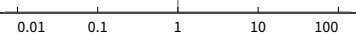
Analysis 5.11. Comparison 5 Sensitivity analyses, Outcome 11 Blinded versus open-label weight Improvement.

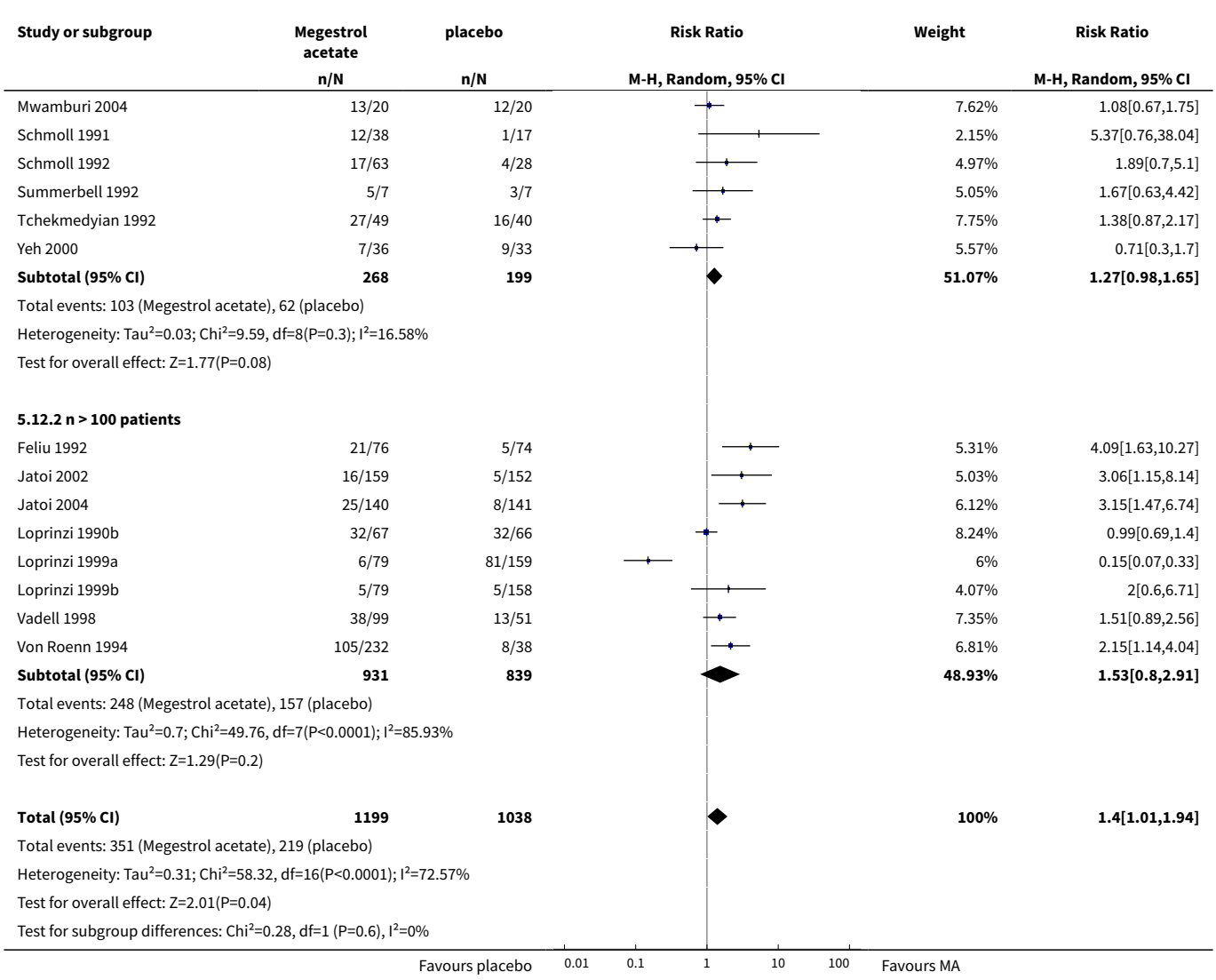
Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.11.1 Blinded studies					
Feliu 1992	21/76	5/74		5.31%	4.09[1.63,10.27]
Fietkau 1996	14/31	6/30		5.84%	2.26[1,5.1]
Jatoi 2002	16/159	5/152		5.03%	3.06[1.15,8.14]
Jatoi 2004	25/140	8/141		6.12%	3.15[1.47,6.74]
Loprinzi 1990b	32/67	32/66		8.24%	0.99[0.69,1.4]
McMillan 1994	4/20	6/18		4.53%	0.6[0.2,1.79]
Tchekmedyian 1992	27/49	16/40		7.75%	1.38[0.87,2.17]
Vadell 1998	38/99	13/51		7.35%	1.51[0.89,2.56]
Von Roenn 1994	105/232	8/38		6.81%	2.15[1.14,4.04]
Yeh 2000	7/36	9/33		5.57%	0.71[0.3,1.7]
Subtotal (95% CI)	**909**	**643**		**62.55%**	**1.63[1.15,2.32]**
Total events: 289 (Megestrol acetate), 108 (Placebo)					
Heterogeneity: Tau^2=0.19; Chi^2=24.82, df=9(P=0); I^2=63.73%					
Test for overall effect: Z=2.73(P=0.01)					
5.11.2 Open-label studies					
Batterham 2001	4/4	5/6		7.6%	1.15[0.71,1.86]
Loprinzi 1999a	6/79	81/159		6%	0.15[0.07,0.33]
Loprinzi 1999b	5/79	5/158		4.07%	2[0.6,6.71]
Mwamburi 2004	13/20	12/20		7.62%	1.08[0.67,1.75]
Schmoll 1991	12/38	1/17		2.15%	5.37[0.76,38.04]
Schmoll 1992	17/63	4/28		4.97%	1.89[0.7,5.1]
Summerbell 1992	5/7	3/7		5.05%	1.67[0.63,4.42]
Subtotal (95% CI)	**290**	**395**		**37.45%**	**1.14[0.53,2.47]**
Total events: 62 (Megestrol acetate), 111 (Placebo)					
Heterogeneity: Tau^2=0.83; Chi^2=37.8, df=6(P<0.0001); I^2=84.13%					
Test for overall effect: Z=0.34(P=0.73)					
Total (95% CI)	**1199**	**1038**		**100%**	**1.4[1.01,1.94]**
Total events: 351 (Megestrol acetate), 219 (Placebo)					
Heterogeneity: Tau^2=0.31; Chi^2=58.32, df=16(P<0.0001); I^2=72.57%					
Test for overall effect: Z=2.01(P=0.04)					
Test for subgroup differences: Chi^2=0.68, df=1 (P=0.41), I^2=0%					



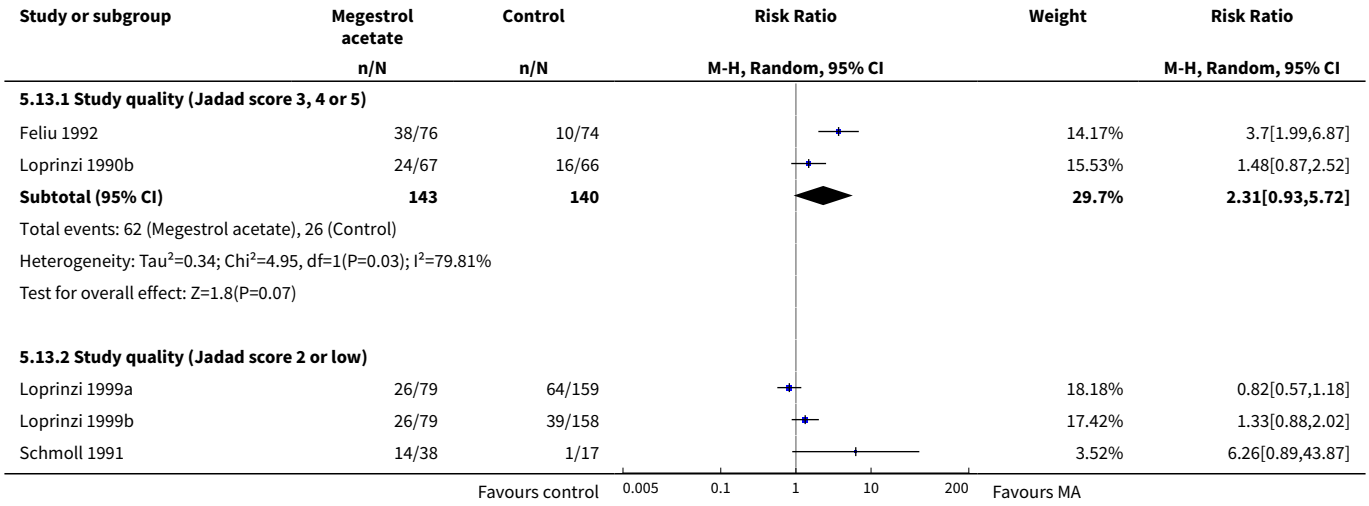
Analysis 5.12. Comparison 5 Sensitivity analyses, Outcome 12 Sensitivity number patients weight improvement.

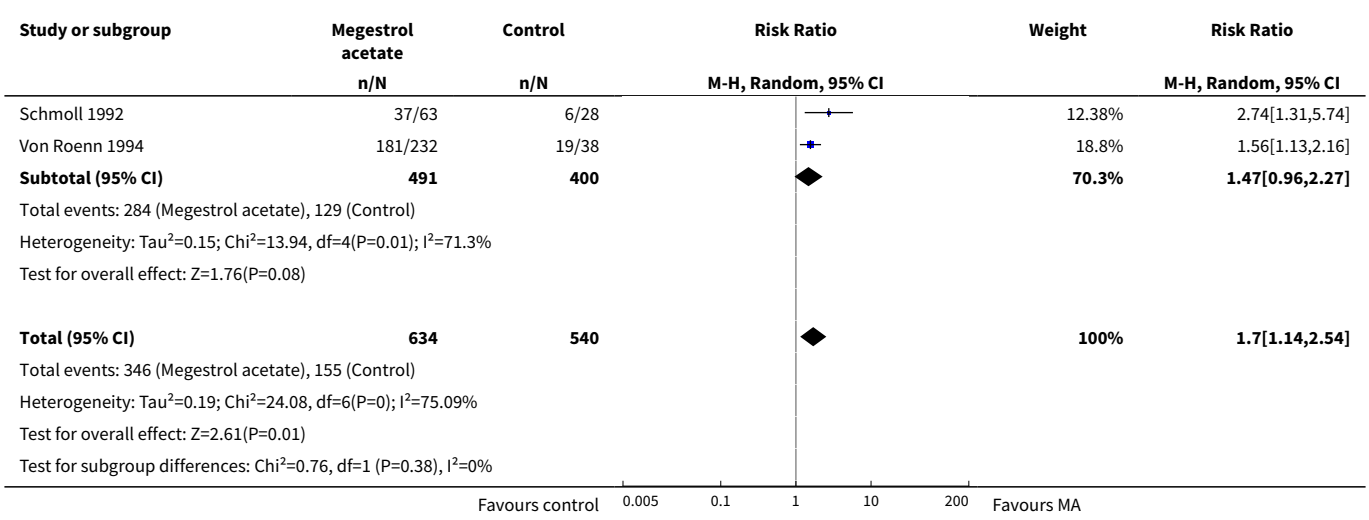
Study or subgroup	Megestrol acetate n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.12.1 n < 100 patients					
Batterham 2001	4/4	5/6		7.6%	1.15[0.71,1.86]
Fietkau 1996	14/31	6/30		5.84%	2.26[1,5.1]
McMillan 1994	4/20	6/18		4.53%	0.6[0.2,1.79]



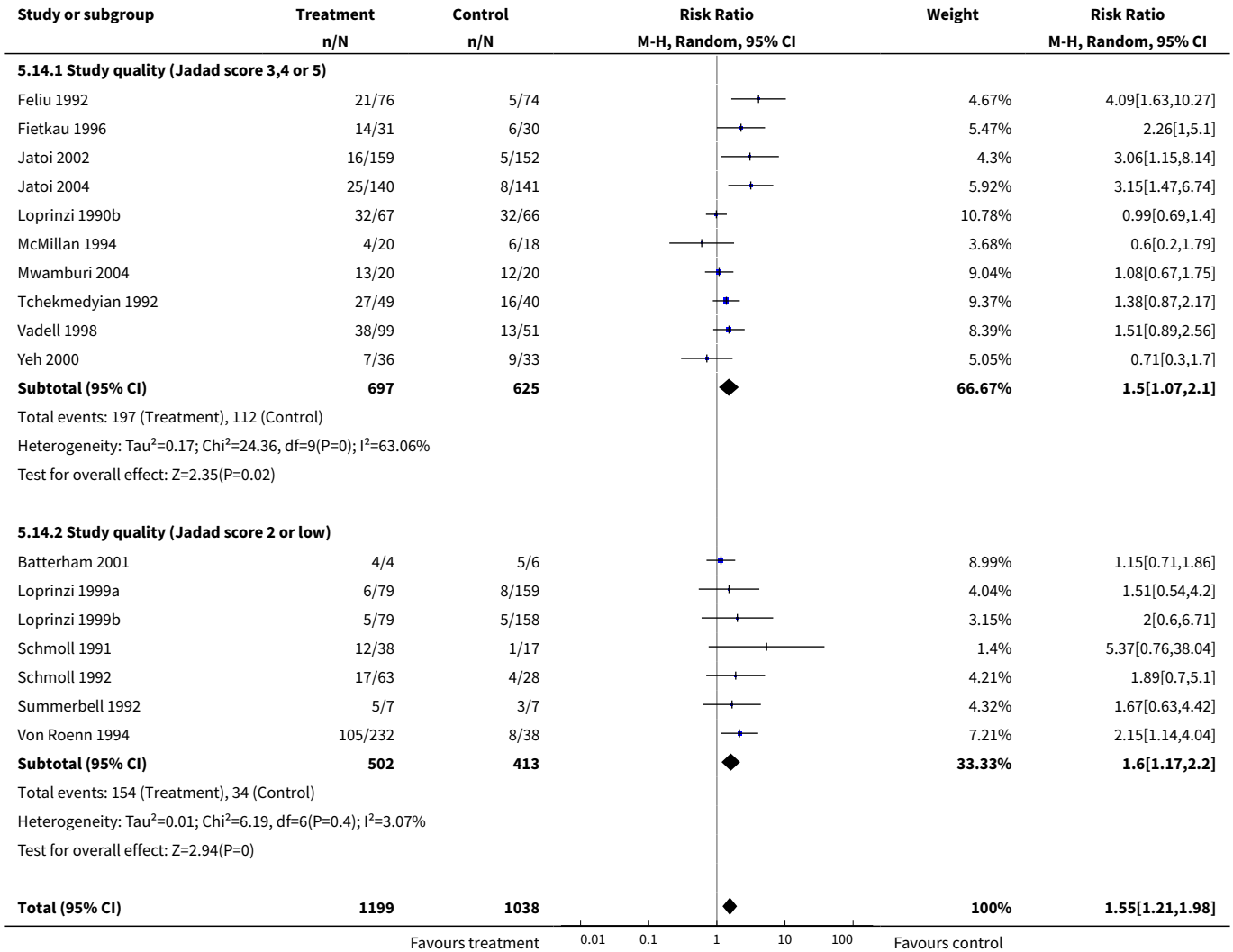


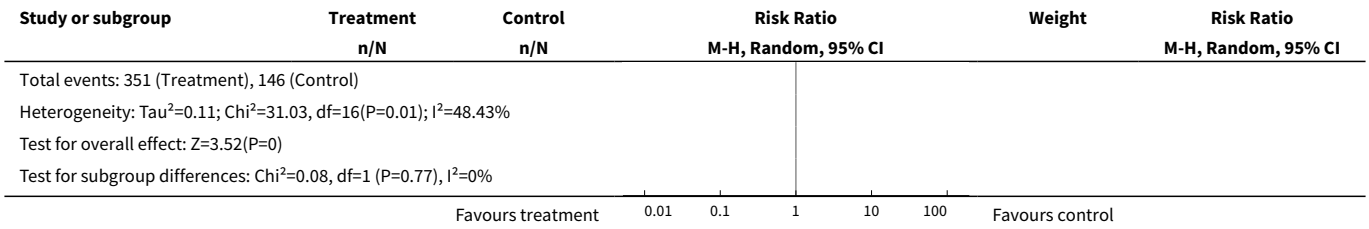
Analysis 5.13. Comparison 5 Sensitivity analyses, Outcome 13 Appetite improvement, study quality.



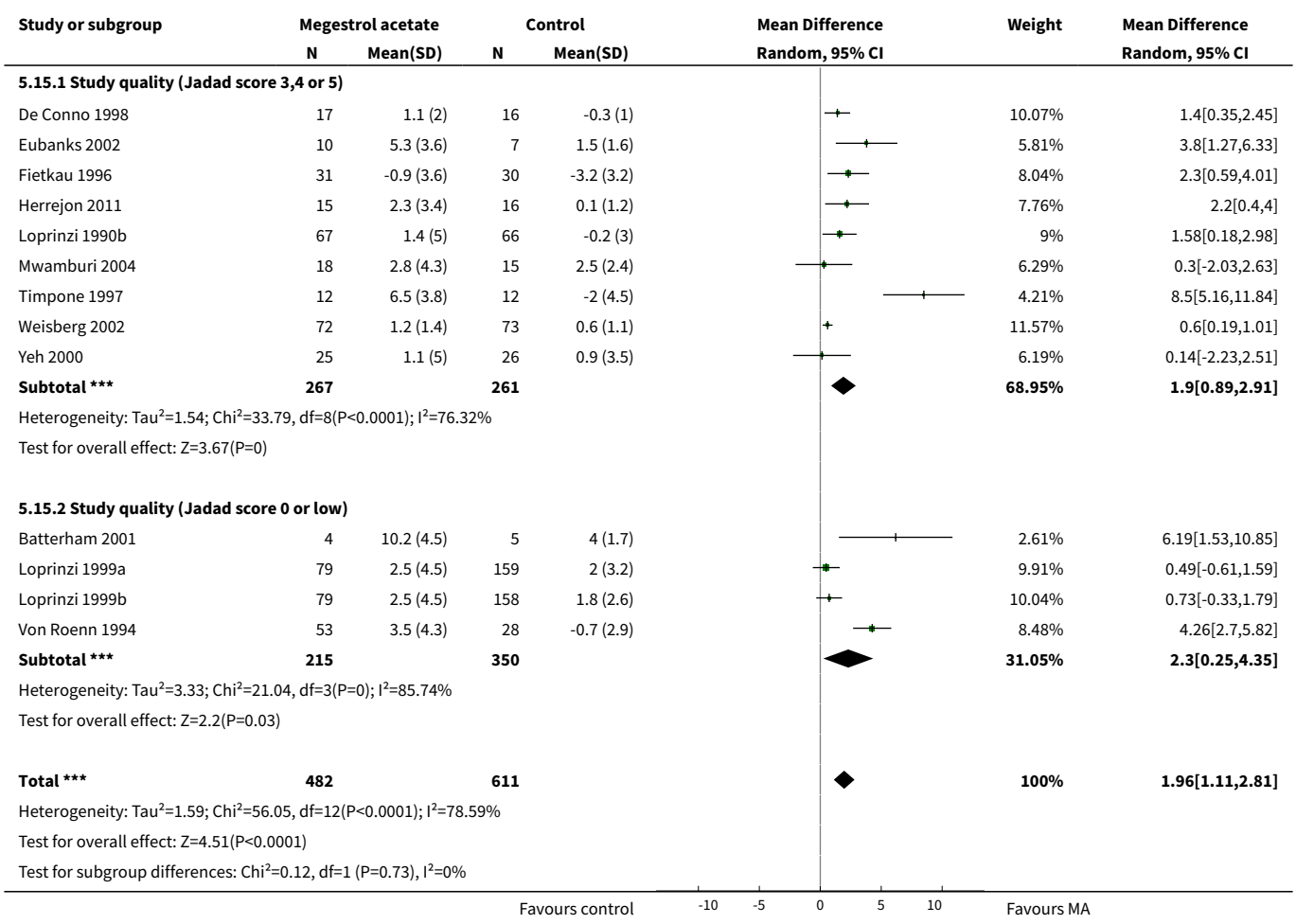


Analysis 5.14. Comparison 5 Sensitivity analyses, Outcome 14 Weight improvement, study quality.

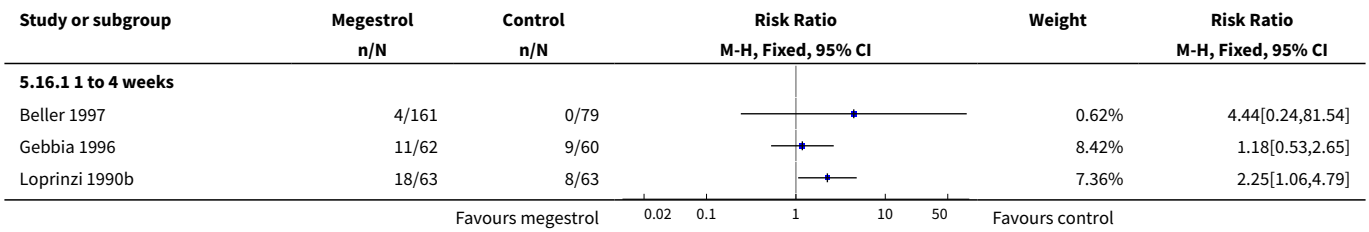


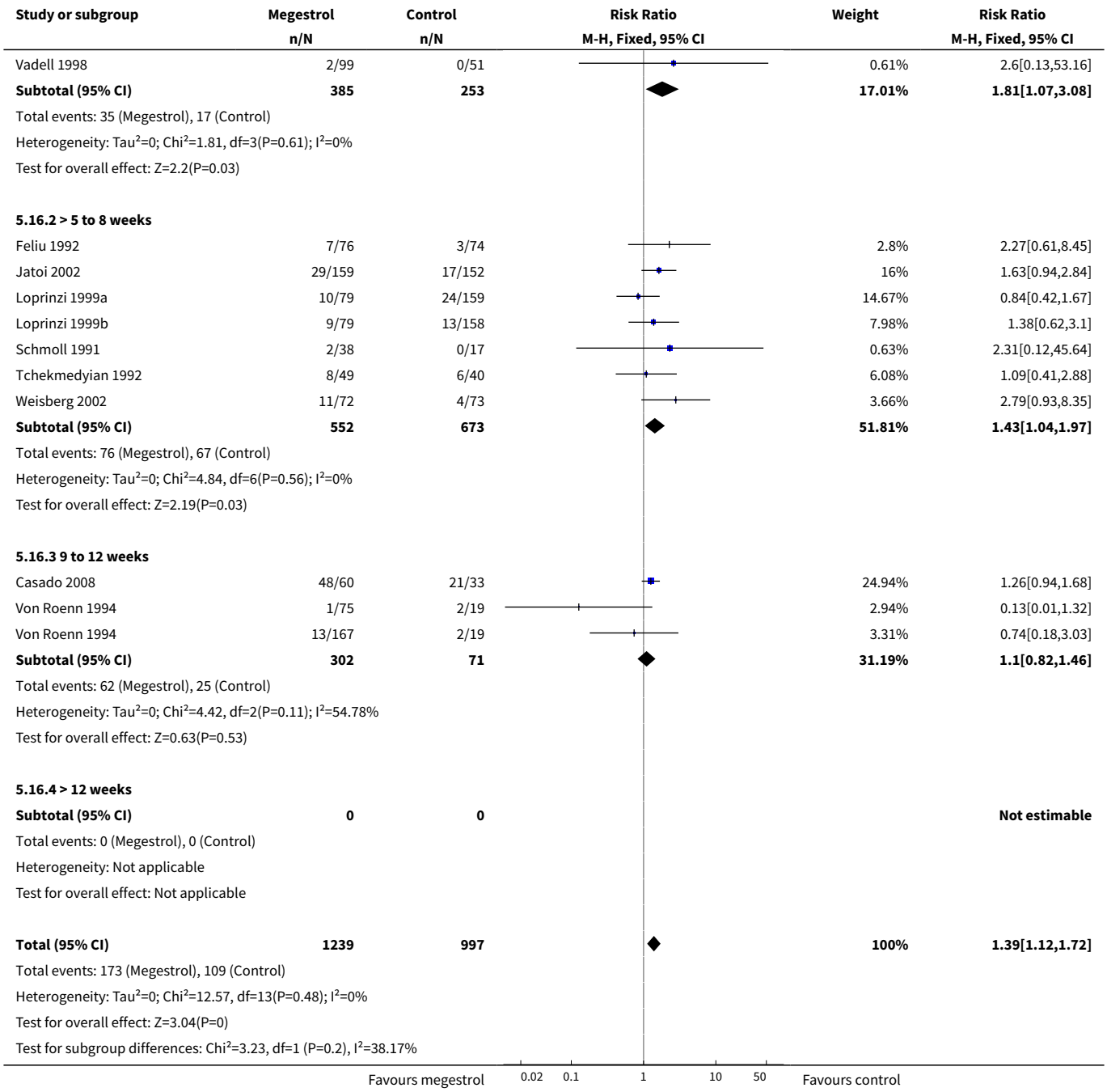


Analysis 5.15. Comparison 5 Sensitivity analyses, Outcome 15 Weight gain, study quality.

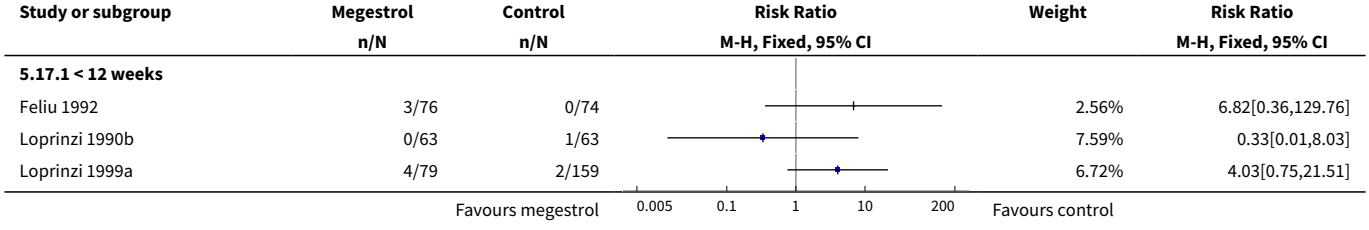


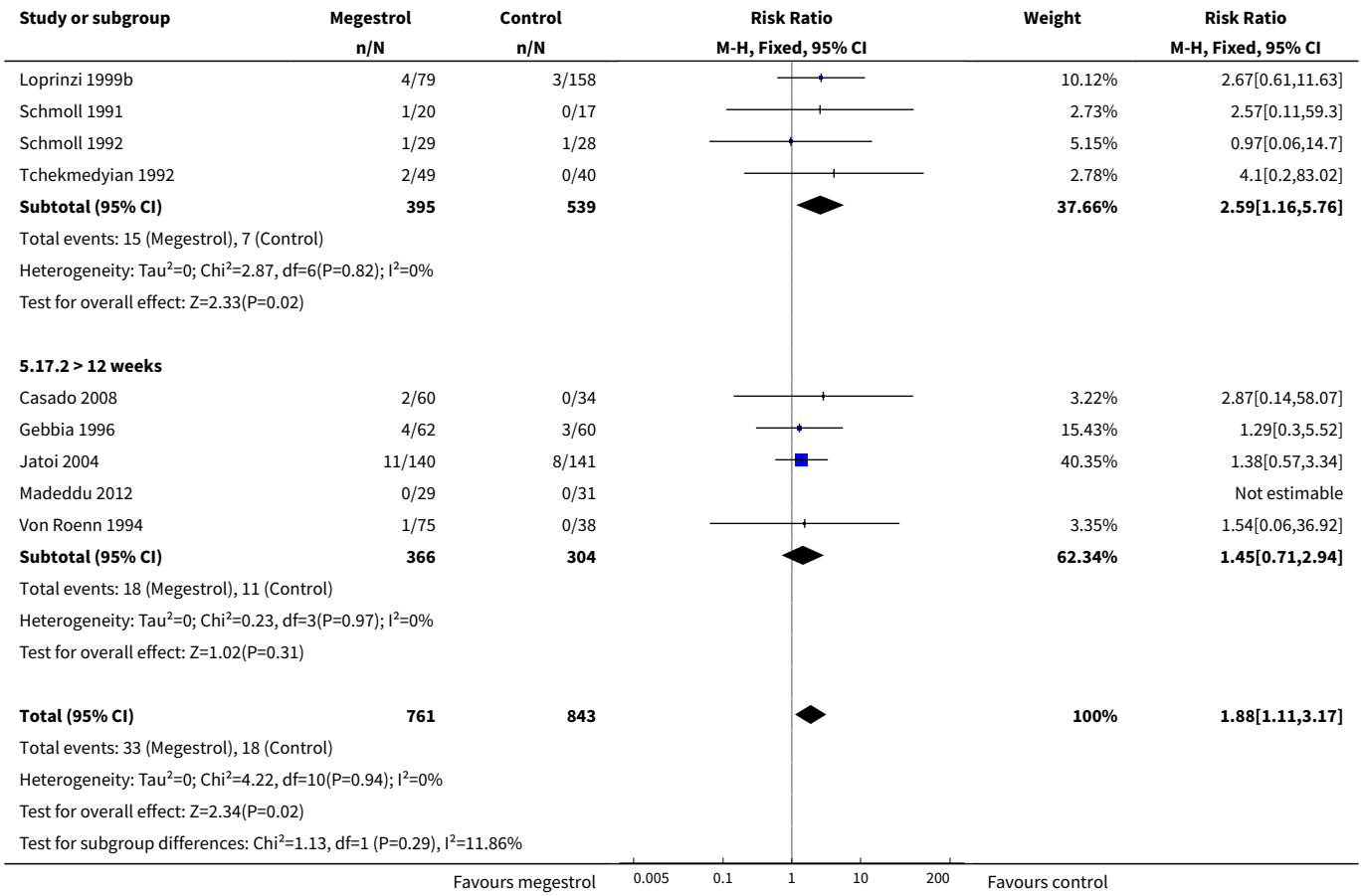
Analysis 5.16. Comparison 5 Sensitivity analyses, Outcome 16 Sensitivity duration oedema.



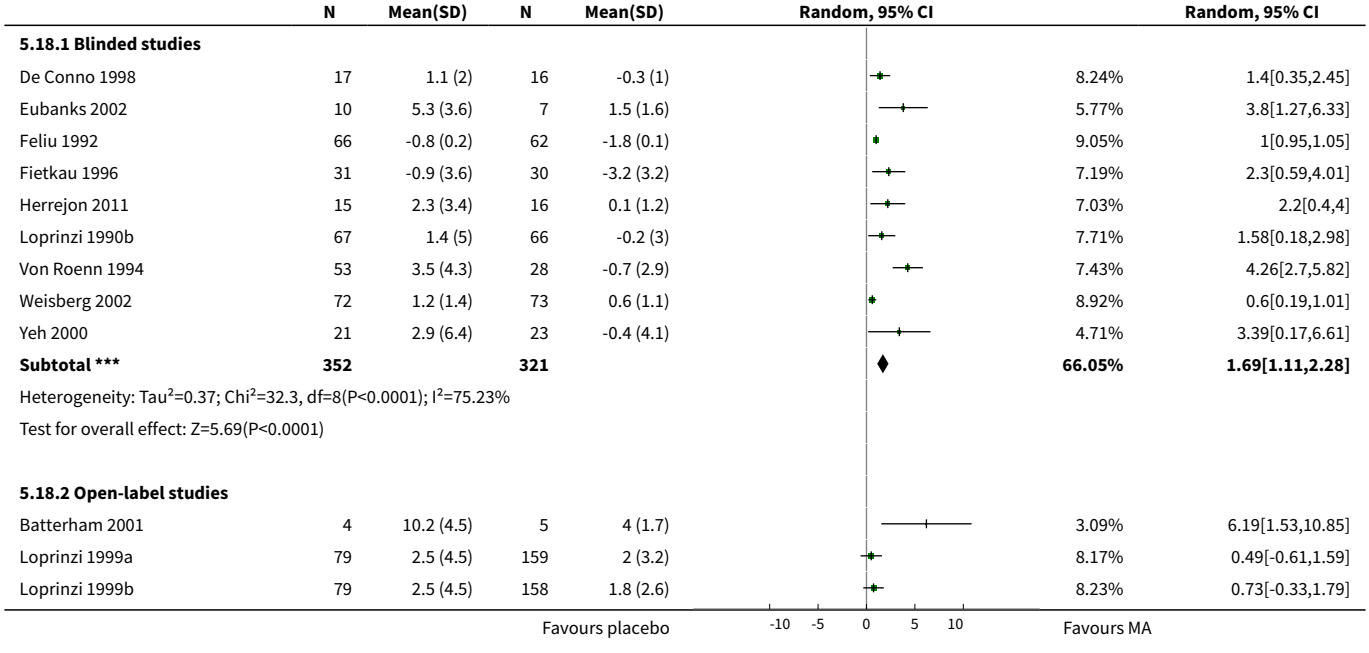


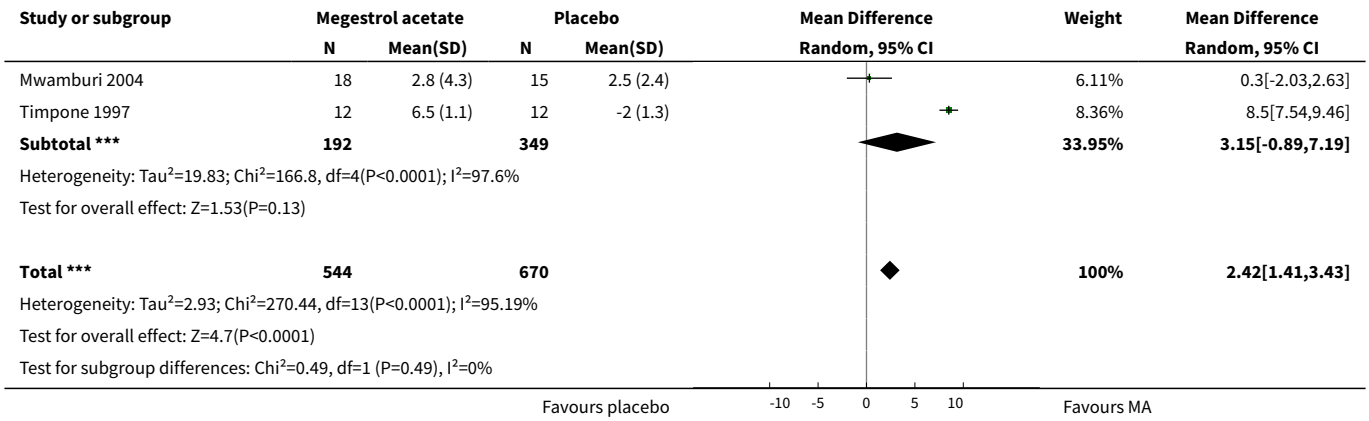
Analysis 5.17. Comparison 5 Sensitivity analyses, Outcome 17 Sensitivity duration thromboembolic phenomena.



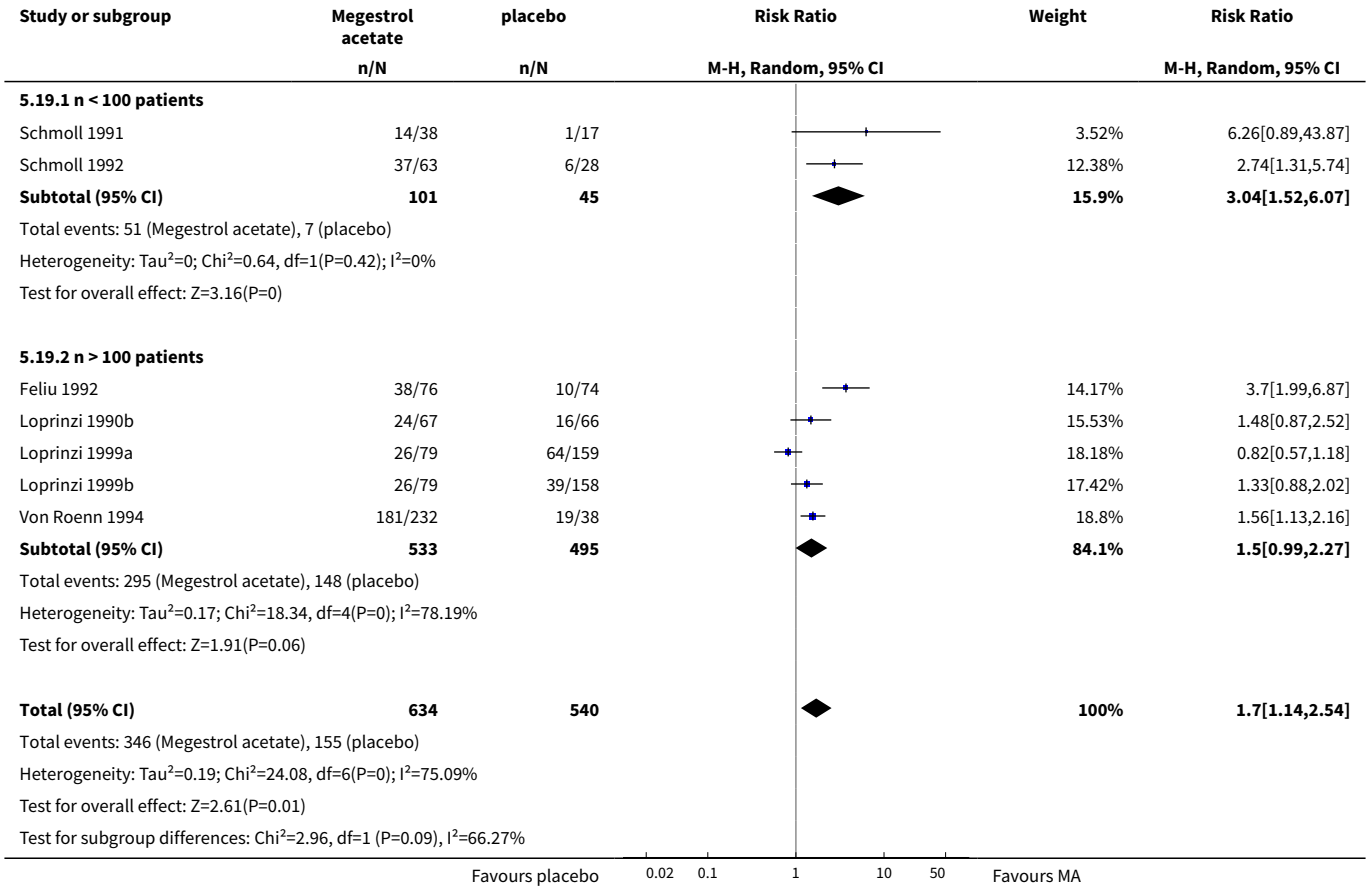


Analysis 5.18. Comparison 5 Sensitivity analyses, Outcome 18 Sensitivity blinded versus open-label weight gain.



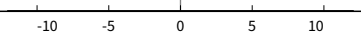


Analysis 5.19. Comparison 5 Sensitivity analyses, Outcome 19 Sensitivity number of patients in trial appetite improvement.



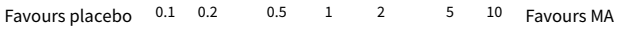
Analysis 5.20. Comparison 5 Sensitivity analyses, Outcome 20 Sensitivity number of patients weight gain.

Study or subgroup	Megestrol acetate N	Megestrol acetate Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.20.1 n < 100 patients							
Batterham 2001	4	10.2 (4.5)	5	4 (1.7)		3.09%	6.19[1.53,10.85]
De Conno 1998	17	1.1 (2)	16	-0.3 (1)		8.24%	1.4[0.35,2.45]
Eubanks 2002	10	5.3 (3.6)	7	1.5 (1.6)		5.77%	3.8[1.27,6.33]
Fietkau 1996	31	-0.9 (3.6)	30	-3.2 (3.2)		7.19%	2.3[0.59,4.01]
Herrejon 2011	15	2.3 (3.4)	16	0.1 (1.2)		7.03%	2.2[0.4,4]
Mwamburi 2004	18	2.8 (4.3)	15	2.5 (2.4)		6.11%	0.3[-2.03,2.63]
Timpone 1997	12	6.5 (1.1)	12	-2 (1.3)		8.36%	8.5[7.54,9.46]
Yeh 2000	21	2.9 (6.4)	23	-0.4 (4.1)		4.71%	3.39[0.17,6.61]
Subtotal ***	**128**		**124**			**50.5%**	**3.45[0.82,6.08]**
Heterogeneity: Tau²=12.85; Chi²=125.09, df=7(P<0.0001); I²=94.4%							
Test for overall effect: Z=2.58(P=0.01)							
5.20.2 n > 100 patients							
Feliu 1992	66	-0.8 (0.2)	62	-1.8 (0.1)		9.05%	1[0.95,1.05]
Loprinzi 1990b	67	1.4 (5)	66	-0.2 (3)		7.71%	1.58[0.18,2.98]
Loprinzi 1999a	79	2.5 (4.5)	159	2 (3.2)		8.17%	0.49[-0.61,1.59]
Loprinzi 1999b	79	2.5 (4.5)	158	1.8 (2.6)		8.23%	0.73[-0.33,1.79]
Von Roenn 1994	53	3.5 (4.3)	28	-0.7 (2.9)		7.43%	4.26[2.7,5.82]
Weisberg 2002	72	1.2 (1.4)	73	0.6 (1.1)		8.92%	0.6[0.19,1.01]
Subtotal ***	**416**		**546**			**49.5%**	**1.13[0.59,1.68]**
Heterogeneity: Tau²=0.26; Chi²=22.04, df=5(P=0); I²=77.31%							
Test for overall effect: Z=4.07(P<0.0001)							
Total ***	**544**		**670**			**100%**	**2.42[1.41,3.43]**
Heterogeneity: Tau²=2.93; Chi²=270.44, df=13(P<0.0001); I²=95.19%							
Test for overall effect: Z=4.7(P<0.0001)							
Test for subgroup differences: Chi²=2.87, df=1 (P=0.09), I²=65.2%							

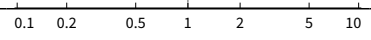


Analysis 5.21. Comparison 5 Sensitivity analyses, Outcome 21 Sensitivity appetite improvement cancer.

Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.21.1 Cancer					
Feliu 1992	38/76	10/74		17.76%	3.7[1.99,6.87]
Loprinzi 1990b	24/67	16/66		18.95%	1.48[0.87,2.52]
Loprinzi 1999a	26/79	64/159		21.12%	0.82[0.57,1.18]
Loprinzi 1999b	26/79	39/158		20.52%	1.33[0.88,2.02]
Schmoll 1991	14/38	1/17		5.57%	6.26[0.89,43.87]
Schmoll 1992	37/63	6/28		16.08%	2.74[1.31,5.74]
Subtotal (95% CI)	**402**	**502**		**100%**	**1.8[1.06,3.04]**
Total events: 165 (Megestrol acetate), 136 (Placebo)					
Heterogeneity: Tau²=0.31; Chi²=24.06, df=5(P=0); I²=79.22%					
Test for overall effect: Z=2.19(P=0.03)					
Total (95% CI)	**402**	**502**		**100%**	**1.8[1.06,3.04]**



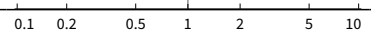
Study or subgroup	Megestrol acetate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 165 (Megestrol acetate), 136 (Placebo)					
Heterogeneity: Tau²=0.31; Chi²=24.06, df=5(P=0); I²=79.22%					
Test for overall effect: Z=2.19(P=0.03)					



Favours placebo Favours MA

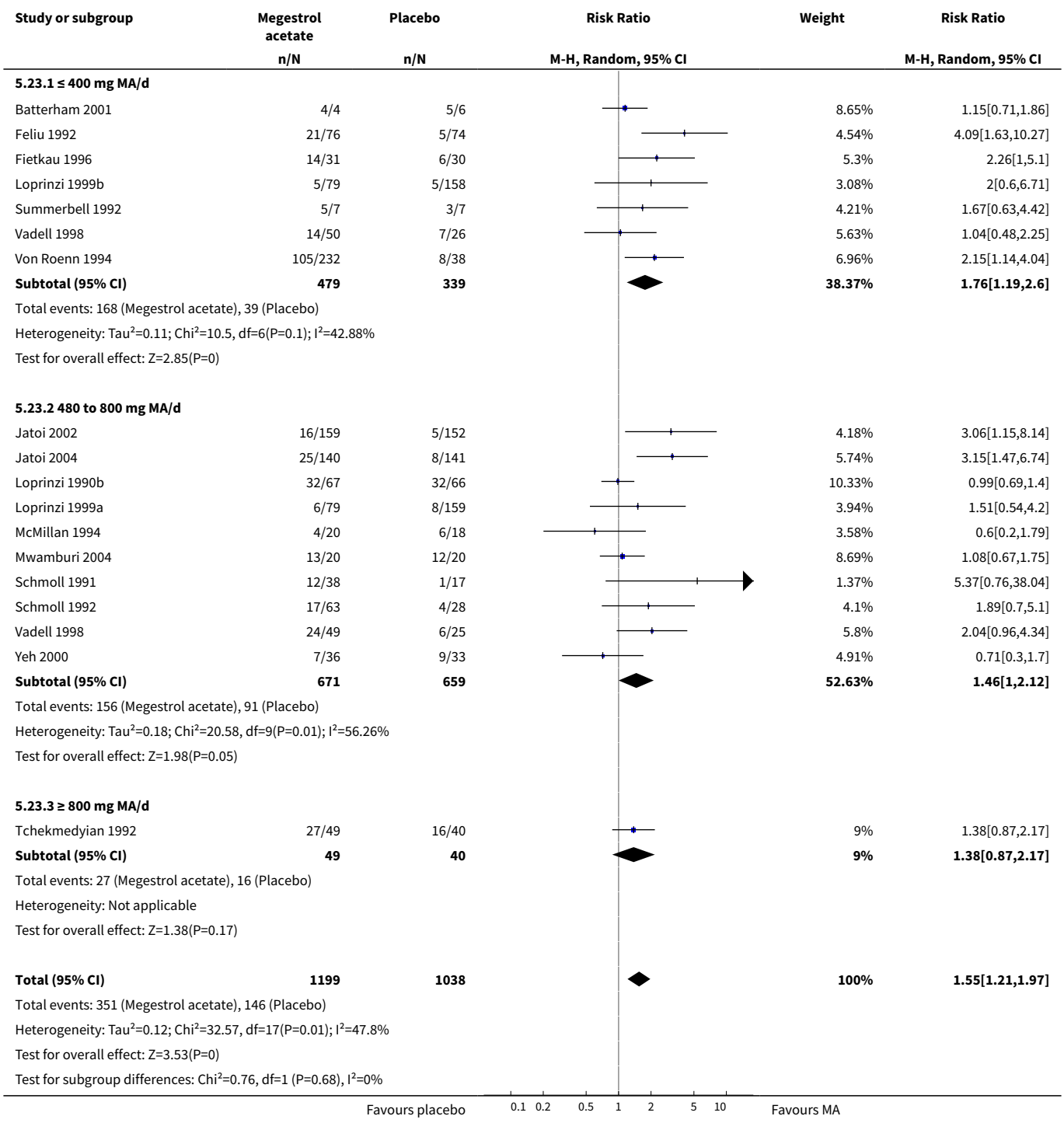
Analysis 5.22. Comparison 5 Sensitivity analyses, Outcome 22 Appetite improvement doses.

Study or subgroup	Megestrol acetate n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.22.1 ≤ 400 mg of MA/d					
Feliu 1992	38/76	10/74		14.17%	3.7[1.99,6.87]
Loprinzi 1990b	24/67	16/66		15.53%	1.48[0.87,2.52]
Von Roenn 1994	181/232	19/38		18.8%	1.56[1.13,2.16]
Subtotal (95% CI)	**375**	**178**		**48.51%**	**1.96[1.17,3.27]**
Total events: 243 (Megestrol acetate), 45 (placebo)					
Heterogeneity: Tau²=0.14; Chi²=6.74, df=2(P=0.03); I²=70.34%					
Test for overall effect: Z=2.56(P=0.01)					
5.22.2 480 to 800 mg of MA/d					
Schmoll 1991	14/38	1/17		3.52%	6.26[0.89,43.87]
Schmoll 1992	37/63	6/28		12.38%	2.74[1.31,5.74]
Subtotal (95% CI)	**101**	**45**		**15.9%**	**3.04[1.52,6.07]**
Total events: 51 (Megestrol acetate), 7 (placebo)					
Heterogeneity: Tau²=0; Chi²=0.64, df=1(P=0.42); I²=0%					
Test for overall effect: Z=3.16(P=0)					
5.22.3 ≥ 800 mg of MA/d					
Loprinzi 1999a	26/79	64/159		18.18%	0.82[0.57,1.18]
Loprinzi 1999b	26/79	39/158		17.42%	1.33[0.88,2.02]
Subtotal (95% CI)	**158**	**317**		**35.6%**	**1.03[0.64,1.67]**
Total events: 52 (Megestrol acetate), 103 (placebo)					
Heterogeneity: Tau²=0.08; Chi²=2.98, df=1(P=0.08); I²=66.44%					
Test for overall effect: Z=0.13(P=0.89)					
Total (95% CI)	**634**	**540**		**100%**	**1.7[1.14,2.54]**
Total events: 346 (Megestrol acetate), 155 (placebo)					
Heterogeneity: Tau²=0.19; Chi²=24.08, df=6(P=0); I²=75.09%					
Test for overall effect: Z=2.61(P=0.01)					
Test for subgroup differences: Chi²=7.1, df=1 (P=0.03), I²=71.82%					



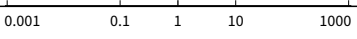
Favours placebo Favours MA

Analysis 5.23. Comparison 5 Sensitivity analyses, Outcome 23 Weight improvement doses.



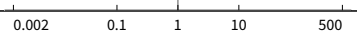
Analysis 5.24. Comparison 5 Sensitivity analyses, Outcome 24 Sensitivity (cancer/other patients) thromboembolic phenomena.

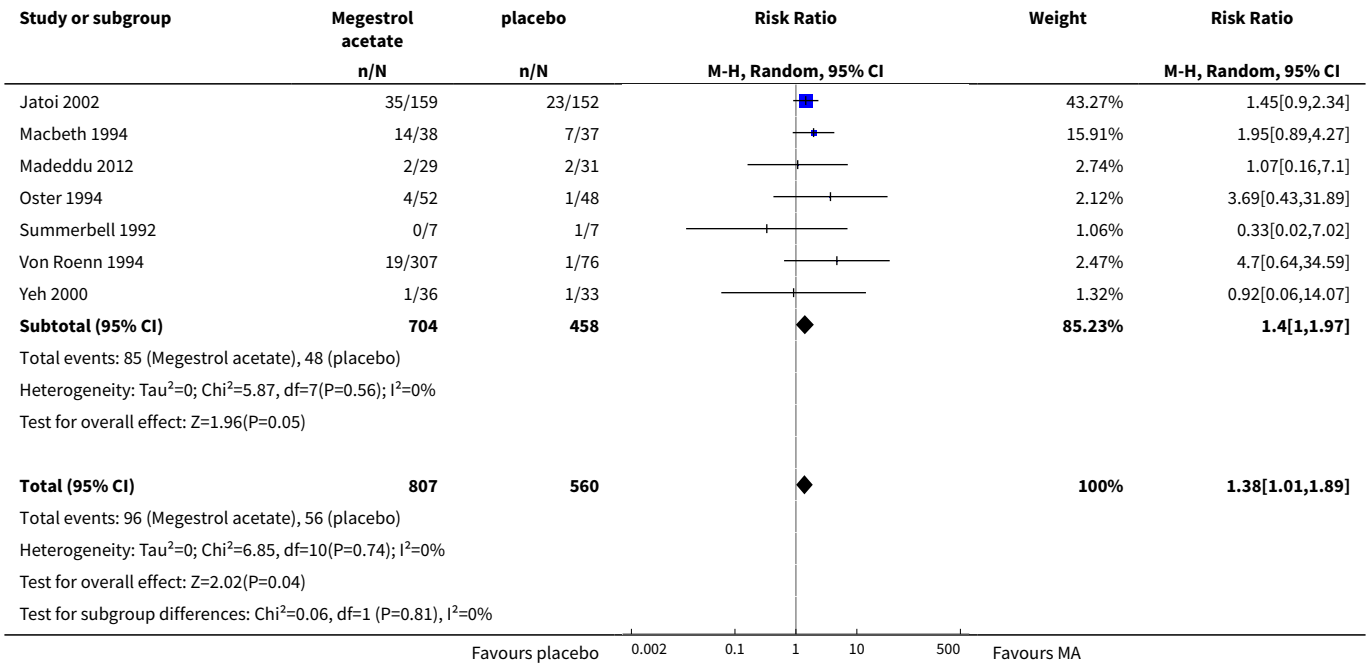
Study or subgroup	Megestrol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.24.1 Cancer patients					
Casado 2008	2/60	0/34		3.22%	2.87[0.14,58.07]
Feliu 1992	3/76	0/74		2.56%	6.82[0.36,129.76]
Gebbia 1996	4/62	3/60		15.43%	1.29[0.3,5.52]
Jatoi 2004	11/140	8/141		40.35%	1.38[0.57,3.34]
Loprinzi 1990b	0/63	1/63		7.59%	0.33[0.01,8.03]
Loprinzi 1999a	4/79	2/159		6.72%	4.03[0.75,21.51]
Loprinzi 1999b	4/79	3/158		10.12%	2.67[0.61,11.63]
Madeddu 2012	0/29	0/31			Not estimable
Schmoll 1991	1/20	0/17		2.73%	2.57[0.11,59.3]
Schmoll 1992	1/29	1/28		5.15%	0.97[0.06,14.7]
Tchekmedyian 1992	2/49	0/40		2.78%	4.1[0.2,83.02]
Subtotal (95% CI)	**686**	**805**		**96.65%**	**1.89[1.11,3.22]**
Total events: 32 (Megestrol), 18 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.21, df=9(P=0.9); I^2=0%					
Test for overall effect: Z=2.33(P=0.02)					
5.24.2 Other patients					
Von Roenn 1994	1/75	0/38		3.35%	1.54[0.06,36.92]
Subtotal (95% CI)	**75**	**38**		**3.35%**	**1.54[0.06,36.92]**
Total events: 1 (Megestrol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					
Total (95% CI)	**761**	**843**		**100%**	**1.88[1.11,3.17]**
Total events: 33 (Megestrol), 18 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.22, df=10(P=0.94); I^2=0%					
Test for overall effect: Z=2.34(P=0.02)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%					



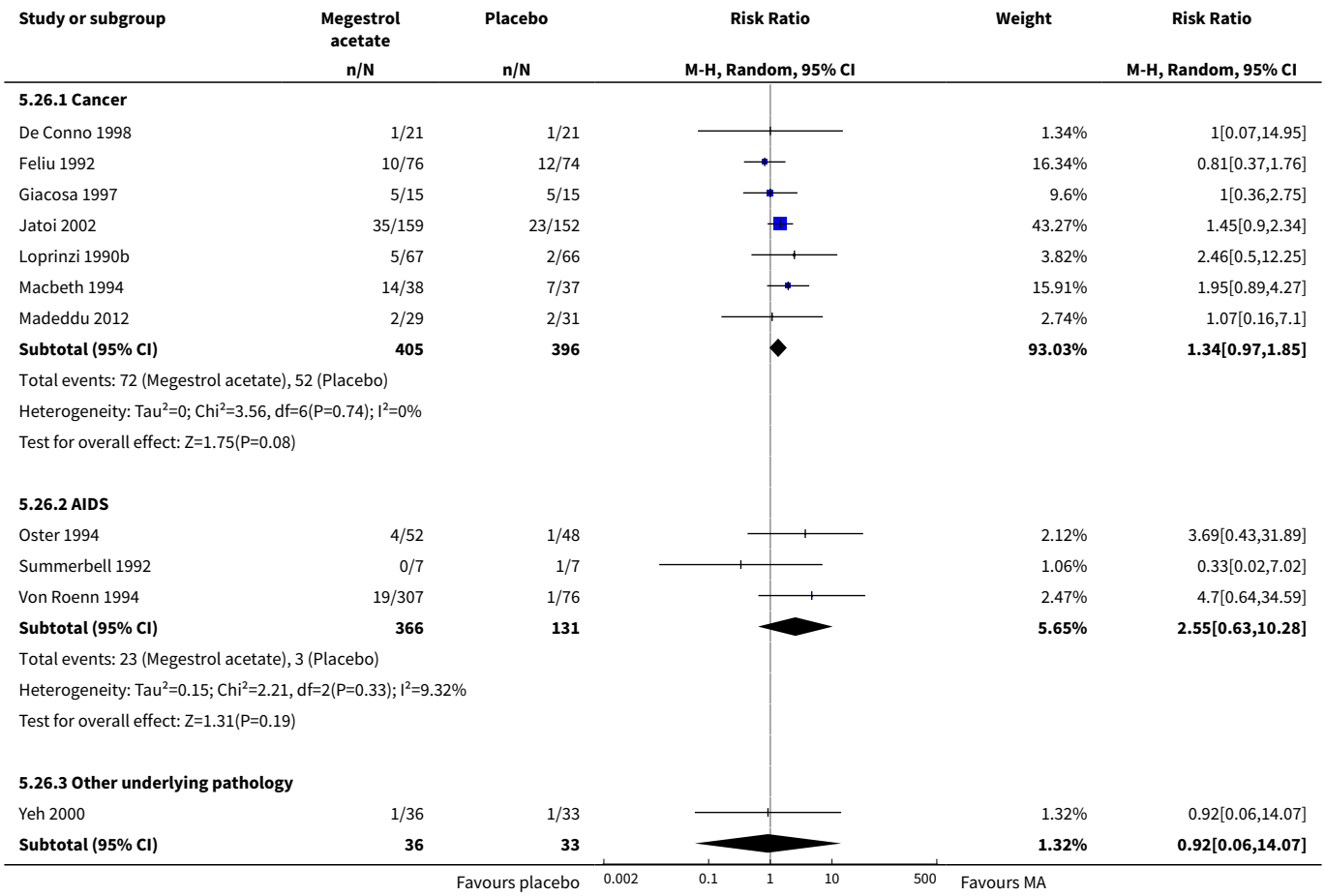
Analysis 5.25. Comparison 5 Sensitivity analyses, Outcome 25 Deaths sensitivity 6 weeks.

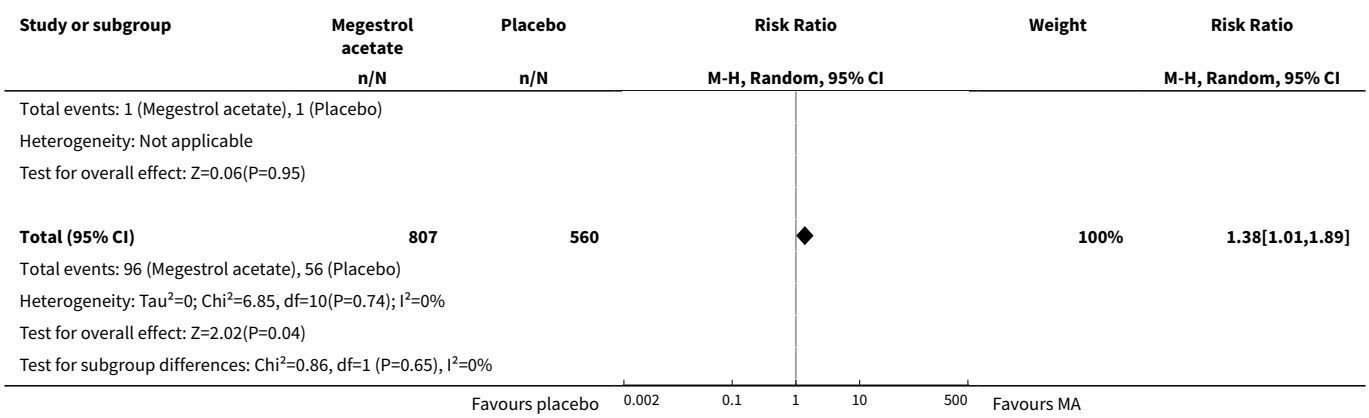
Study or subgroup	Megestrol acetate n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.25.1 < 6 weeks					
De Conno 1998	1/21	1/21		1.34%	1[0.07,14.95]
Giacosa 1997	5/15	5/15		9.6%	1[0.36,2.75]
Loprinzi 1990b	5/67	2/66		3.82%	2.46[0.5,12.25]
Subtotal (95% CI)	**103**	**102**		**14.77%**	**1.26[0.56,2.86]**
Total events: 11 (Megestrol acetate), 8 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=2(P=0.63); I^2=0%					
Test for overall effect: Z=0.56(P=0.58)					
5.25.2 > 6 weeks					
Feliu 1992	10/76	12/74		16.34%	0.81[0.37,1.76]





Analysis 5.26. Comparison 5 Sensitivity analyses, Outcome 26 Deaths sensitivity/pathology.





ADDITIONAL TABLES

Table 1. Patient condition and numbers recruited to each trial

Study	Lung cancer	Gastrointestinal and pancreas	Head and neck cancer	Gynaecological cancer	Other cancer	AIDS	COPD	Cystic fibrosis	Elderly
Batterham 2001						15			
Beller 1997	48	106	18		68				
Casado 2008	35	21	11	6	21				
De Conno 1998	21	10	6		5				
Eubanks 2002								17	
Feliu 1992	75	36	9		30				
Fietkau 1996			64						
Gambardella 1998	No data	No data	No data	No data	No data				
Gebbia 1996	50	22	40		10				
Giacosa 1997	3	10			5				
Heckmayr 1992	66								
Herrejon 2011							40		
Jatoi 2001	208	139			121				
Jatoi 2004	166	141			114				
Lesser 2006	No data	No data	No data	No data	74				
Loprinzi 1990b	42	53			38				
Loprinzi 1994	130	111			101				
Loprinzi 1999	192	171	114						
Mwamburi 2004						40			

Table 1. Patient condition and numbers recruited to each trial *(Continued)*

McMillan 1994		26			12				
Macbeth 1994	75								
Madeddu 2012	12	24	13	7					
Oster 1994						100			
Sancho-Cuesta 1993									
Schmoll 1991									
Schmoll 1992									
Tchekmedyian 1992	27	23	4		35				
Von Roenn 1994						270			
Ulutin 2002	119								
Timpone 1997						50			
Vadell 1998	75	35	5	8	27				
Weisberg 2002							145		
Yeh 2000									69
Total	**1342**	**928**	**284**	**21**	**907**	**475**	**185**	**17**	**69**

APPENDICES

Appendix 1. Cochrane Pain, Palliative and Supportive Care Group's Trial Register

#1	MeSH descriptor Cachexia, this term only
#2	MeSH descriptor Anorexia, this term only
#3	anorexi*
#4	cachex* or cachectic
#5	MeSH descriptor Weight Loss explode all trees
#6	MeSH descriptor Appetite, this term only
#7	weight or wasting or appetite
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9	MeSH descriptor Megestrol explode all trees
#10	megestrol
#11	(#9 OR #10)
#12	(#8 AND #11)
Issue 3 2011; we have rerun the searches from Issue 3 to Issue 5, 2012	

Appendix 2. MEDLINE search strategy in OVID

1 Cachexia/
2 Anorexia/
3 anorexi*.mp.
4 (cachex* or cachectic).mp.
5 exp Weight Loss/
6 Appetite/
7 (weight or wasting or appetite).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp Megestrol/
10 megestrol.mp.

(Continued)

11 9 or 10
12 randomised controlled trial.pt.
13 controlled clinical trial.pt.
14 randomized.ab.
15 placebo.ab.
16 drug therapy.fs.
17 randomly.ab.
18 trial.ab.
19 groups.ab.
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 8 and 11 and 20
Key: mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier; pt = publication type; ab = abstract: fs = floating subheading; MEDLINE 1948 to July week 3, 2011; we have rerun the searches from 2011 to May week 2 2012

Appendix 3. EMBASE search strategy in OVID

1	cachexia/
2	anorexia/
3	anorexi*.mp.
4	(cachex* or cachectic).mp.
5	weight reduction/
6	appetite/
7	(weight or wasting or appetite).mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	megestrol/
10	megestrol acetate/
11	megestrol.mp.
12	9 or 10 or 11

(Continued)

13 crossover procedure/
14 randomised controlled trial/
15 single blind procedure/
16 random*.mp.
17 factorial*.mp.
18 (crossover* or cross over* or cross-over).mp.
19 placebo*.mp.
20 (doubl* adj blind*).mp.
21 (singl* adj blind*).mp.
22 assign*.mp.
23 allocat*.mp.
24 volunteer*.mp.
25 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 8 and 12 and 25
Key: mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]: 1980 to 2011 week 29; we have rerun the searches from 2011 to 2012 week 19

FEEDBACK

Feedback submitted, 26 September 2018

Summary

Name: Anna Sutherland
Email Address: anna.sutherland@cochrane.nhs.uk
Affiliation: Oxford University Hospitals Foundation Trust
Role: ST5 Palliative Medicine

I have found this review very helpful in informing practice and have certainly seen a trend away from the use of megesterol in clinical practice in light of these results. However, I feel this review would be even more accessible and useful if the GRADE assessment for each outcome (and what that means about the certainty of the results in clinical practice) were reported in the abstract and the text of the review as the summary of findings table is not as accessible to all readers. For example: "In patients who take MA, approximately one in four will have an increase in their appetite (very low quality), one in 12 will have an increase in their weight (very low quality) and one in 23 will die (very low quality)."

Reply

The Editors thank Anna Sutherland for her comments. We have liaised with the authors who would like to draw your attention to their co-publication of this review available here: https://doi.org/10.1002/jcsm.12292.

This review was last published in 2013, and was stabilised in 2017. At the next update, we will consider incorporating your suggestions into the abstract, which comply with the current MECIR standards.

Contributors

Feedback Editor Hayley Barnes, Co-ordinating Editor Christopher Eccleston, and Managing Editor Anna Erskine.

WHAT'S NEW

Date	Event	Description
14 March 2019	Feedback has been incorporated	See Feedback.
7 July 2017	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 2, 2005

Date	Event	Description
24 June 2012	New citation required and conclusions have changed	In the current update we decided not to include cross-over studies and to include only trials with patients who clearly had some previous weight loss or any definition of cachexia-anorexia syndrome. None of the original authors remaining in this review. Eleven studies were excluded: Bruera 1990; Bruera 1998; Chen 1997; Erkurt 2000; Lai 1994; Marchand 2000; McQuellon 2002; Pardo 2003a; Rowland 1996; Westman 1999; Zeca 1995. Thirteen new studies were included: Casado 2008; Giacosa 1997; Herrejon 2011; Lesser 2006; ; Macbeth 1994; Madeddu 2012; Mwamburi 2004; Schmoll 1991; Summerbell 1992; Timpone 1997; Wanke 2007. We included 35 trials which represent 3963 patients studied for effectiveness and 3240 for safety. We could not use the data from the included trials Lesser 2006 and Gambardella 1998, therefore 863 fewer patients were ultimately studied in this update. There are changes to the previous conclusions of the review. More than 40 side effects were studied. Oedema, thromboembolic phenomena and deaths were more frequent in the patients treated with megestrol acetate (MA). Despite MA being approved for use in AIDS patients by US Food and Drug Administration, this drug failed to show weight improvement and weight gain when compared with other drugs. MA compared with placebo was effective in one trial in AIDS patients. MA could be prescribed to improve appetite in the context of palliative medicine, but it should be emphasised that this drug probably will not recover full weight loss, nor increase quality of life and it is related to adverse events, including increased mortality.
24 June 2012	New search has been performed	The search was updated on 7 May 2012.
11 May 2011	Amended	Contact details updated.

Date	Event	Description
30 October 2008	Amended	Converted to new review format.
20 August 2007	New search has been performed	For the update for Issue 4, 2007 the following changes were made: Four new studies and three abstracts were identified, two of these studies were full text and were included in this updated review (Jatoi 2004; Ulutin 2002). These trials added 540 additional participants to the review. Two of these studies were excluded (Macbeth 1994; Yeh 2004). There was no change to the previous conclusions of the review.

CONTRIBUTIONS OF AUTHORS

VR put forward the idea of updating the review.
JH performed the search.
VR located trials.
EL and VR applied the inclusion/exclusion criteria.
RC and JLG extracted the data and appraised the quality of the trials.
Data entry into RevMan was carried out by SB.
VR and SB produced the first draft.
All of the team wrote and approved the final draft.

DECLARATIONS OF INTEREST

No one involved in this review has any conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Instituto de Investigaciones Epidemiológicas, Academia Nacional de Medicina de Buenos Aires, Argentina.

External sources

- No sources of support supplied

NOTES

We performed full searches in February 2015, and April and December 2016, intending to complete a full update, but we did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acquired Immunodeficiency Syndrome [complications]; Anorexia [*drug therapy] [etiology]; Appetite Stimulants [adverse effects] [*therapeutic use]; Cachexia [*drug therapy] [etiology]; Megestrol Acetate [adverse effects] [*therapeutic use]; Neoplasms [complications]; Randomized Controlled Trials as Topic; Syndrome

MeSH check words

Humans